A.M.A. Archives of
OPHTHALMOLOGY

AUGUST 1956

VOLUME 56 NUMBER 2

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Ophthalmic Pharmacology and Toxicology
W. Morton Grant

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1. Check the DISTANCE CENTERS to be sure they coincide with the patient's distance PD horizontally and *vertically*.

2. Examine the patient's eyes for both VERTICAL and HORIZONTAL ASYMMETRY and ascertain that any difference is incorporated in the position of the bifocal.

3. Hyperopes must have ADDITIONAL DECENTRATION of the bifocal segment to compensate for the base out prism created by the distance portion of the lens.

4. Incorrect BIFOCAL HEIGHT is probably the most common problem of bifocal wearers. Segments cause trouble when fitted either too high or too low for visual requirements. Because of prismatic effect, myopes tend to wear their bifocal higher and hold their reading material lower than hyperopes, although a myope is more likely to notice and therefore complain about a segment which intrudes on his distance field.

5. Induced VERTICAL IMBALANCE found at the reading point must be corrected if it exceeds one prism diopter. This can be achieved by the use of slab-offs, dissimilar segments or prism segments.

6. Glasses should be ADJUSTED so that they are horizontal with and equidistant from the eyes. They should be fitted close to the eyes in order to increase the angular field of the bifocal and make the division line less noticeable to the patient. Pantoscopic tilt (on all but heavy myopic prescriptions) helps bring the division line under and away from the patient's distance field.

All of these "bifocal troubles" are discussed individually in other Scientific Corner articles. Copies are available upon request.

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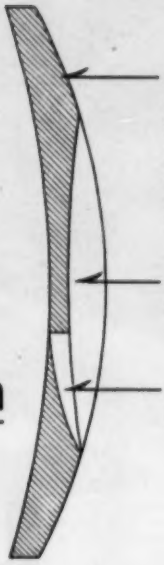
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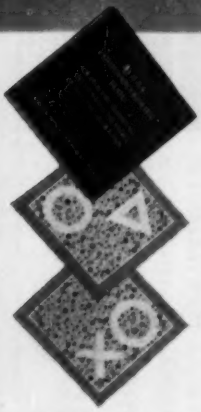

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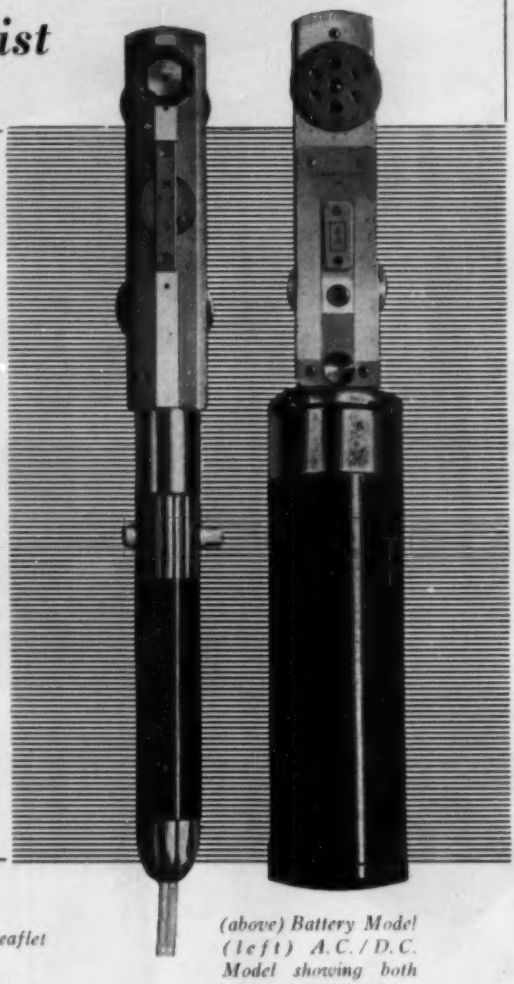

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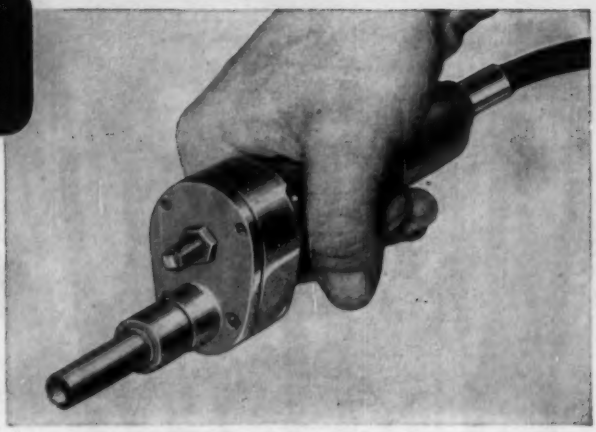

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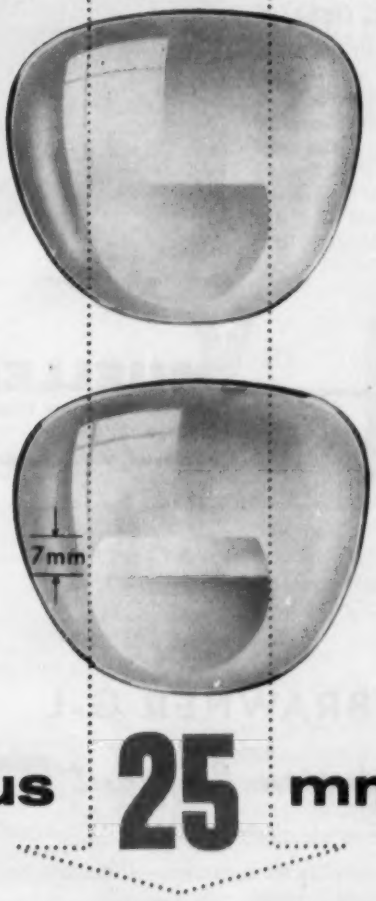

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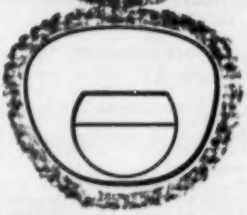

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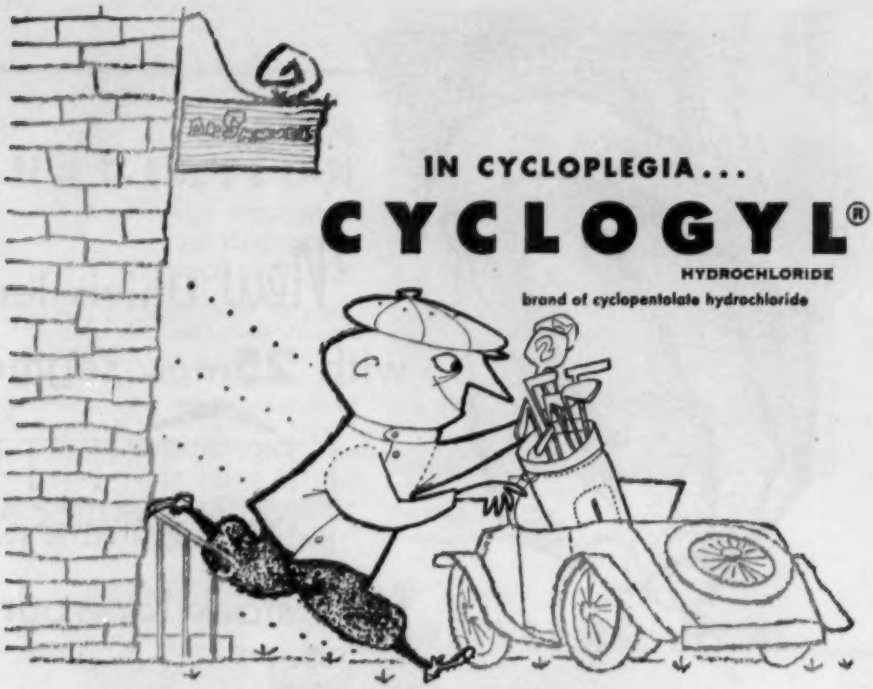

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1. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. 38:831 *(Dec.) 1954.*

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Ehrlich, L. H.: New York J. Med. 53:3015 *(Dec. 15) 1953.*

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Cycloplegia – One drop 1.0%, in each eye (or two drops of 0.5%) produces maximal cycloplegia in 30-60 minutes. Recovery time is normally 4-12 hours spontaneously. Pilocarpine reduces recovery time. In deeply pigmented eyes, 2 drops of 1.0% in each eye, instilled 10 minutes apart, achieves satisfactory cycloplegia in 98% of cases.

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Ocular Findings in Meningiomas of the Tuberculum Sellae

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and
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The chiasmal syndrome (primary optic atrophy with bitemporal field defects in adult patients showing an essentially normal sella), so commonly produced by suprasellar meningioma, was described in 1927 by Holmes and Sargent [1] and confirmed in 1929 and 1930 by Cushing.* A tumor in this position arising from the tuberculum sellae may give as few indications of its presence as any lesion with which the neurosurgeon has to deal. A temporal field cut in one or both eyes plus optic atrophy in the more affected eye may seem very inadequate grounds for suggesting a craniotomy, especially since the sella may not be eroded, headache may not be severe, and evidence of pituitary dysfunction may be lacking. Nevertheless, if these tumors are to be dealt with successfully the decision to operate must be based on these ocular findings alone. When visual symptoms have become marked, and visual loss, field defects, or optic atrophy is pronounced, the tumor may well have reached sufficient size to involve the adjacent carotid arteries and complete removal may be difficult and dangerous. In such instances permanent loss of vision is an almost inevitable consequence in at least one eye, though the patient may survive for long periods of time despite incomplete removal of the tumor.

This report concerns 30 patients all of whom have had neurosurgical intervention and pathologic verification of meningiomas arising from the region of the tuberculum sellae. Nineteen patients survived surgery and had an average follow-up of 7 years, ranging from 2 months to 28 years. Five patients died of recurrence within 4 years, with an average follow-up of 2.4 years. Six patients died in the postoperative period (Table 1). Of the 24 patients who survived surgery, 3 had complete removals and were alive for periods of 22, 6, and 6 years, respectively. The remaining patients had incomplete removals and survived for postoperative periods varying from several months to 28 years. Ten patients are alive 10 years after surgery (Table 2).

Further evaluation showed that three patients with complete removals had good postoperative vision and a long follow-up, seven patients had incomplete removal

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From the Department of Neurosurgery and Ophthalmology, Hospital of the University of Pennsylvania.

* References 2 and 3.

with good postoperative vision, and the remaining patients with long follow-up periods had incomplete removals with progression to blindness but led useful lives. Five patients had incomplete removals with death from recurrence within four years after surgery. Two of these had useful vision in one eye until they died. Four patients had incomplete removals with operative survival but inadequate follow-up. Six patients died immediately postoperatively (Table 3).

TABLE 1.—*Results in Total Group*

	Cases, No.
Alive, av. follow-up 7 yr. (2 mo.-28 yr.)	19
Died p.o. of recurrence, av. follow-up 2.4 yr.	5
P.o. fatalities	6
Total patients	30

TABLE 2.—*Results in Patients Who Survived Surgery*

	Cases, No.
Complete removals, alive (22,6,6 yr.)	3
Incomplete removals, alive (28,21,20,19,18,16,14,13,13, 10,6,6,2,2 yr., 3 mo., 2 mo.)	16
Incomplete removals, died of recurrence (av. 2.4 yr.)	5

TABLE 3.—*Results of Operation*

	Cases, No.
Comp. rem., p.o. vision good, long follow-up	3
Incomp. rem., p.o. vision good, long follow-up	7
Incomp. rem., blind useful, long follow-up	5
Incomp. rem., died from recurrences 2.4 yr. p.o.	5
Incomp. rem., no follow-up	4
P.o. death (2 hem., 3 edema, 1 infection)	6

Preoperative Findings

Two-thirds of the patients were white females. The average age of all the patients was 45 years. Five patients were under 20 years of age, the youngest being 7.

The ocular manifestations were the earliest and most important complaint in all instances. Visual loss was invariably asymmetric in its progression and was accompanied initially by central hemianopic temporal visual field defects. Slowly developing blindness in one eye with diminution of acuity is then accompanied by a temporal field defect in the opposite eye. There was no extraocular motor paresis in any patient in this group. Exophthalmos was notably absent. In no instance was papilledema noted before surgical intervention. In seven patients signs of hypopituitarism were present, but in only two were these manifestations grossly in evidence. Headaches were present in 13 but had only reached serious proportions in 4. In all of these patients the tumors were large when verified. Other neurologic signs were completely absent except for anosmia, which was present bilaterally in 3 cases, unilaterally in 1, and absent in 19 in whom it was tested.

The preoperative history was uniformly one of visual field loss, which, dated from the first visual symptom, might be from 2 months to 30 years in duration (Table 4). Seventeen of thirty patients had visual symptoms of less than one

year's duration prior to surgery. Definite pallor of the optic nerves as well as loss of vision and field were present when these signs were first observed and recorded. It is evident that the history was misleading in many instances. These signs must have been present for long periods before they were discovered and their importance realized. Thirteen patients had visual symptoms and signs varying from 3 to 30 years. Thus, loss of visual acuity and optic atrophy of long duration does not preclude the presence of a tumor. A majority of patients were found to have one eye seriously affected. However, loss of central visual acuity in the remaining eye was the determining factor in bringing them to the physician. Eight of the ten patients in the survival group with long follow-up and good final vision had long preoperative histories. The duration of the history does not necessarily

TABLE 4.—*Preoperative Ocular Manifestations*

Survivals	Duration of Visual Symptoms	Vision	Optic Atrophy			Visual Fields		
			Bilateral	Unilateral	Absent	Early	Mod. Adv.	Late
A. Comp. removal, good p.o. vision (3 cases)	5 mo. to 8 yr.	6/6 to 6/12—3 eyes C.F. to L.P.—3 eyes	3	0	0	1	2	0
Incomp. removal, B. good p.o. vision (7 cases)	2 mo. to 18 yr.	6/6 to 6/60—8 eyes 6/100 to no L.P.—6 eyes	4	1	2	4	2	1
Incomp. removal, C. prog. to blind p.o. & useful long lives f.u. (5 cases)	2 mo. to 10 yr.	6/15 to 6/2.7—2 eyes 6/100 to no L.P.—8 eyes	4	0	1	0	1	4
Incomp. removal, death of disease D. within 4 yrs p.o. (5 cases)	6 mo. to 8 yr.	6/12 to 6/60—5 eyes 6/100 to no L.P.—5 eyes	5	0	0	0	2	3
Incomp. removal, E. inadequate follow-up (4 cases)	3 yr. to 30 yr.	6/75 to 6/60—4 eyes 6/150 to no L.P.—4 eyes	2	2	0	0	3	1
P.o. deaths Comp. removal (2 cases) Incomp. removal, (4 cases)	1 yr. to 15 yr.	6/6 to 6/30—4 eyes 6/150 to no L.P.—8 eyes	6	0	0	1	3	2
Total	Av. 6.5 yr.	6/6 to 6/60—26 eyes 6/100-no L.P.—34 eyes	24	3	3	6	13	11

point to a poor prognosis. These facts indicate that meningiomas, in this as in other regions, grow very slowly. They produce their symptoms over a long period of time and are in general unnoticed by the patient until profound visual loss has occurred. This inherent slow growth of these tumors is responsible not only for the remarkably long preoperative histories but for the long survival period, 28 years in one instance, after incomplete removal of the tumor.

The type of progression of the visual loss in these patients is of interest. Four had a rapid and fluctuating loss of vision typical of retrobulbar neuritis. After these initial changes in visual acuity and fields these patients eventually settled down to a slow progressive loss of vision in one or both eyes. Twenty-two patients had an insidious onset with slow progressive visual loss over long periods of time.

In a majority of instances visual loss was profound in at least one eye before operation was performed. Seventeen of thirty patients had vision in one eye of less than 6/100, and seven patients had lost useful vision in both eyes. With

rare exceptions, it was found that when the vision was reduced to below 6/100 progression to blindness was the rule even after release of pressure by surgery. Exceptions to this were two patients who had vision of 6/15 and 6/27, respectively, and eventually became blind in spite of surgery. In addition, two patients who had complete removal of their tumor and good visual acuity postoperatively had vision as low as hand movements and counting fingers before operation. A careful examination of their records shows that the field defects were essentially dense central scotomas (Table 4).

Twenty-seven of the thirty patients showed evidence of optic atrophy before operation. This defect was bilateral and unequal in 14 instances and bilateral and equal in 9, and 3 patients had only unilateral pallor (Table 4). Although these patients were all thought to have optic atrophy in one or both eyes before operation,

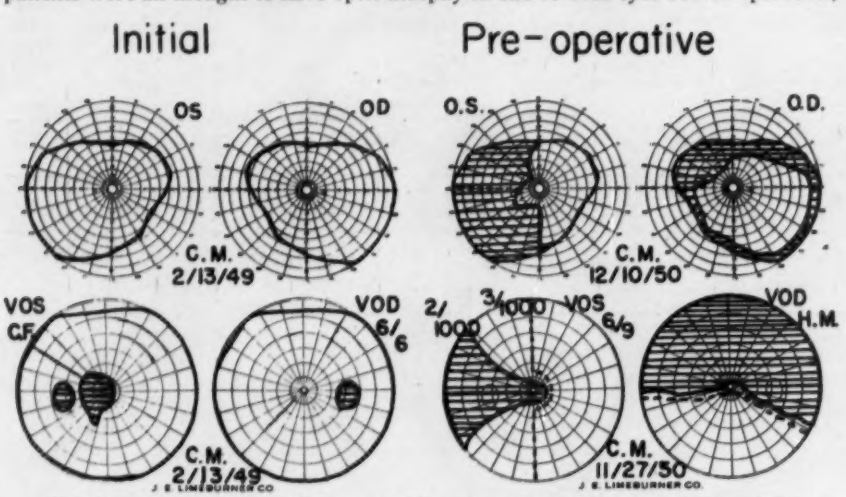

Fig. 1.—Initial peripheral fields to 1/330 white test object normal. Central field to 2/1000 white and 5/1000 red show only a central scotoma in the left eye with vision reduced to counting fingers. Fields done within two weeks before surgery showed a temporal defect on the left and an altitudinal defect on the right. Postoperatively V.O.D. No. C.P. V.O.S.=6/6.

in seven instances the discs were described as normal postoperatively. A further discrepancy noted was that low visual acuity did not necessarily correspond with those eyes that had the more pronounced pallor of the disc.

Visual field defects were present in all these patients. The early field changes were predominantly present in the central isopters as temporal hemianopic defects. They were complete or incomplete and most often were very irregular in outline. The patient was aware of the visual field defect when the scotomatous area became dense enough to affect central visual acuity. The initially affected eye often progressed almost to complete blindness before a defect in the fellow eye was noted. This asymmetric field loss emphasizes the fact that these tumors press predominantly upon the nasal fibers in the optic nerve and not the crossing fibers in the chiasm. Bitemporal hemianopic defects of a symmetrical character produced by primary pituitary tumors are a rarity in this group of patients. The bizarre character of the fields is illustrated in Figure 1. In this patient there was a rapid onset of symptoms, with a fluctuating loss of vision and central field affecting one eye and then the other, with complete remissions characteristic of retrobulbar

neuritis. Eventually progressive loss of vision and the appearance of optic atrophy led to neurosurgical intervention.

Six patients (20%) with field defects designated as early had unilateral or bilateral temporal cuts which were not severe. Five of these six had excellent vision and field postoperatively. One died following surgery. Thirteen patients (43%) had moderately advanced field defects. These patients were blind or near-blind in one eye and showed no change (two patients) or early field defects in the other eye. Six recovered good vision; one became blind postoperatively. In three instances ophthalmologic examination postoperatively was inadequate, and three died after surgery. The remaining 11 patients had advanced changes in one eye and complete hemianopic defects with pronounced loss of central vision in the remaining eye down to blindness or near-blindness with a residual field (Fig. 2).

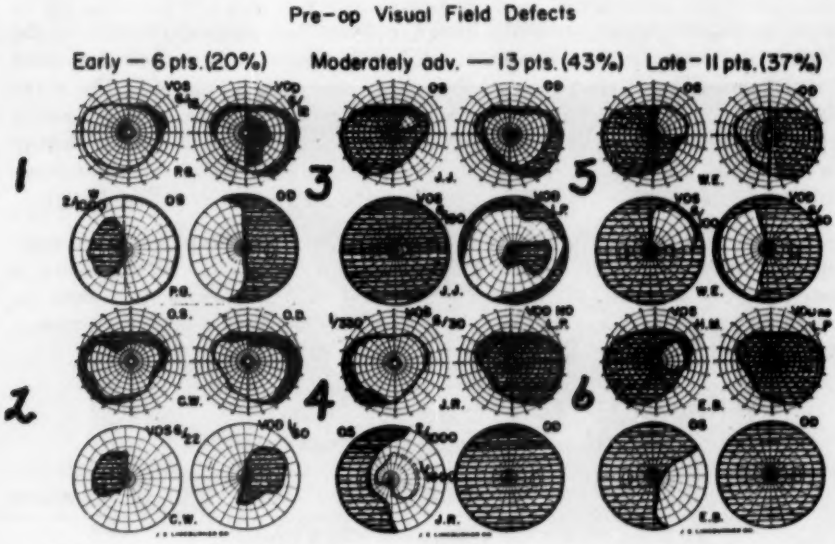

Fig. 2.—Preoperative visual field defects in six patients. In each patient the peripheral field is arranged above and the central field below. *1* and *2* are examples of patients with early defects; *3* and *4* illustrate moderately advanced defects, and *5* and *6* show far-advanced type of field changes.

Eight became blind or near-blind within two years after surgery. One lived 13 years with good vision restored to one eye, and two died following operation. The preoperative visual field is the most important single finding as regards the probable benefit to be obtained from operation. It has already been stated that visual acuity can be very poor and the optic nerves abnormally pale and yet visual function following operation may be good. However, if field loss is extensive before operation the prognosis for good visual function is poor (Table 5).

Six of the thirty patients had normal skull x-rays. Four of these patients had large inoperable tumors and had very poor postoperative results. It is therefore possible for plain x-rays to be negative even when a large tumor is present. Of the 24 patients with changes in the plain x-ray of the skull, 7, or 23% of the total group, had advanced destruction of the posterior clinoids and dorsum sellae with enlargement of the sella turcica. Of this group, three had good vision and long life without progression of their disease up to 14 years after operation, de-

TABLE 5.—*Comparison of Preoperative Visual Fields with Final Vision and Field*

Preop. Field Defects			Final Vision and Field		
Early	Mod. Adv.	Late	Good 6/6	Fair 6/15—6/30	Poor or Near Blind O2
6			5 (2 both eyes) (3 1 eye only)		(1 died p.o.)
	13		5 (1 eye only)	1	1 (3 died p.o.) (3 poor f.u.)
		11			8 (2 died p.o.) (1 poor f.u.)

spite incomplete tumor removal. Eleven patients had marked changes in the dorsum and posterior clinoids without sellar enlargement, and six showed minimal but definite evidence of erosion of these bony structures (Table 6). The x-ray findings, therefore, can be very deceiving as indicative of the size and extent of growth of these tumors. Seven patients had calcifications of varying density in the region above the sella. In the presence of specific ocular manifestations, with or without other x-ray changes, this can be an important diagnostic sign.

Arteriography was used in four cases and was helpful in each instance in making a definite diagnosis. It should be used in all cases suspected of having a tumor in this area. Encephalography was used in five cases, and in three in which the tumor was large this study was helpful. Two patients with large tumors had encephalograms that were described as normal.

TABLE 6.—*X-Ray Findings Preoperatively*

Survivals	Plain Films					Arteriogram	Encephelogram
	Adv. Erosion with Enlarged Sella	Mod. Adv. Erosion Dorsum & Post. Clinoid with Sella Enlarged	Dorsum Sella & Post. Clinoid Erosion Sl. with Sella Enlarged	Calcification	Normal		
Comp. rem. with good p.o. vision & follow-up (3 cases)	0	1	1	1	0	1 diagnostic	0
Incomp. rem. with good p.o. vision & follow-up (7 cases)	3	2	1	1	1	0	0
Incomp. rem. with p.o. progress. to blind., but long & useful lives & follow-up (5 cases)	2	2	1	1	0	1 diagnostic	1 diagnostic
Incomp. rem. with death from disease within 4 yr. (5 cases)	1	1	1	1	2	0	1 diagnostic
Incomp. rem & inadequate follow-up (4 cases)	0	3	0	0	1	2 diagnostic	1 diagnostic
Deaths							
Comp. removals (2 cases)	0	1	1	2	0	0	1 normal
Incomp. removals (4 cases)	1	1	1	1	2	0	1 normal
Totals	7	11	6	7	6	4 diagnostic	3 abnormal 2 normal

Outcome of Cases

The outcome of these cases is clearly outlined in Tables 1 through 3. Decompression of at least one optic nerve without complete removal of the tumor was accomplished in 18 of the 30 patients. Eighteen patients had right transfrontal craniotomy, and eight had their operation on the left. In four instances bilateral transfrontal operations were performed. The operation is usually carried out from the right side, regardless of the ophthalmologic findings, because of the greater facility with which the right-handed neurosurgeon can operate on this side. In addition, interference with the circulation of the right cerebral hemisphere will result in less serious neurologic deficit in right-handed patients. In some instances the operation was performed on the side of better vision when the opposite eye was blind or near-blind. This approach facilitated decompression of the nerve on that side and thus preserved vision in the better eye. The optic nerve usually is humped over or pushed aside by the tumor (Fig. 3). Too often,

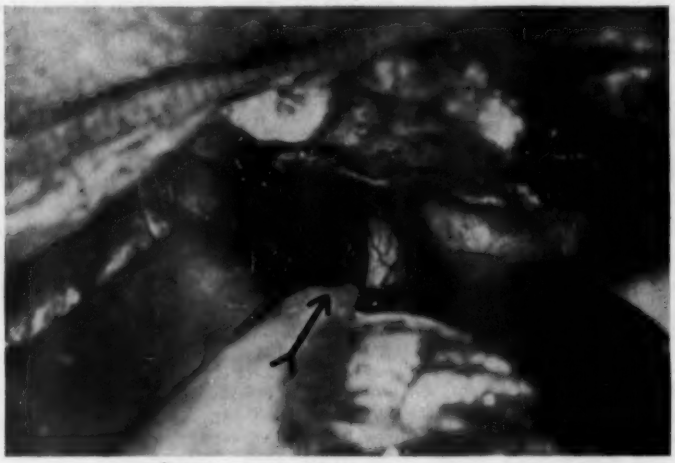

Figure 3

however, one or both nerves are inseparable from or encircled by the neoplasm. The internal carotid and anterior cerebral arteries may or may not be visible. If neither nerves nor blood vessels are seen, experience dictates that the operator remove enough of the tumor to establish its character and withdraw. If the nerves and arteries are visible, total extirpation can be attempted and, with luck, will be successful. The chief hazard of removal of any tumor in this region is direct damage to the internal carotid. If the carotid must be occluded, immediate and permanent hemiparesis results. In view of the slow growth of these tumors and the longevity with good visual results postoperatively, this is a high price to pay for complete removal.

Summary

Thirty patients with meningiomas of the tuberculum sellae were studied in detail, and correlation was made between their preoperative findings, with particular reference to the ocular manifestations, and the operative and eventual visual results. Visual symptoms were the initial and important manifestations

in each instance. Slow progressive loss of vision accompanied by central visual field defects in the temporal field of the remaining eye and optic atrophy were characteristic. Visual loss may come on rapidly or insidiously. Thereafter, a slow progressive course is most usual, but in some instances fluctuating vision and fields in the early phases of the disease may mimic retrobulbar neuritis. In no instance was papilledema noted. Preoperative visual loss varied from several months to 30 years, but the duration of these symptoms had no significant bearing on eventual outcome as regards visual function, morbidity, or mortality. In general, low visual acuity before operation accompanied by severe visual field impairment indicated a poor prognosis for vision after surgery. Optic atrophy and loss of vision over long periods, regardless of a slow or rapid onset or of progressive or fluctuating course in the absence of other neurologic signs, does not preclude the presence of a tumor. The fact that these tumors are slow-growing accounts for the long preoperative histories and for the fact that many of these patients led useful lives with good vision for long periods of time after surgery, despite incomplete removal. The absence of x-ray changes in the skull does not in any way prove that a neoplasm even of large size is not present. It was surprising to learn that marked destructive changes in and around the sella are compatible with long life and good vision after operation, even with incomplete removal of the tumor. Arteriography is stressed as an excellent diagnostic aid in the suspected presence of this lesion.

In conclusion, therefore, a plea is made for a more complete evaluation of any patient with optic atrophy and visual loss of unexplained origin, despite duration of findings, in whom there is a defect in the opposite temporal field and in whom skull x-rays either show normal findings or changes indicative of increased pressure as manifest by erosion of the dorsum sellae or posterior clinoids.

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Report of Five Hundred Patients Examined for Low Vision

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Five hundred patients were examined for low-vision lenses at the Lighthouse (The New York Association for the Blind.) Lenses were prescribed for 240, all of whom were later interviewed to decide whether or not the lenses were beneficial.* The examiner concluded that 173 patients were rehabilitated to an acceptable degree.

The results of this project showed two significant facts: 1. A correction for lenses seemed to make a worthwhile improvement in 48% of the patients examined. 2. Of those for whom lenses were prescribed, 72% were judged to have a successful result by the standards of both the examiner and the patient.

The criteria for success or failure depended upon an interview with the patient after he had worn his correction for two months. This interval seemed advisable in order to avoid the influence of initial enthusiasm. The decision of success or failure depended upon the answers to the following questions:

1. How long have you had your present glasses?
2. How often do you use them?
3. How long do you use them at one time?
4. For what purposes do you use them?

Some decisions were made with ease. In cases where a decision was difficult the patient was interviewed again at a later date.

The types of ocular pathology chiefly responsible for the low vision in those cases in which lenses were prescribed are indicated in Table 1.

TABLE 1.—*Types and Incidence of Ocular Pathology Causing Low Vision*

Ocular Pathology	Total Cases, No.	Number Successful	Percentage Successful
Glaucoma	33	21	64
Optic atrophy	30	22	73
Miscellaneous	21	17	81
Corneal opacities	20	14	70
Myopic chorioretinal degeneration	20	16	80
Macular degeneration	19	15	79
Cataracts	18	13	72
Chorioretinitis	18	11	61
Albinism	17	16	94
Postoperative aphakia (congenital cataracts)	16	13	81
Retinitis pigmentosa	10	3	30
Diabetic retinopathy	10	6	60
Postoperative retinal detachments	5	4	80
Keratoconus	3	2	67

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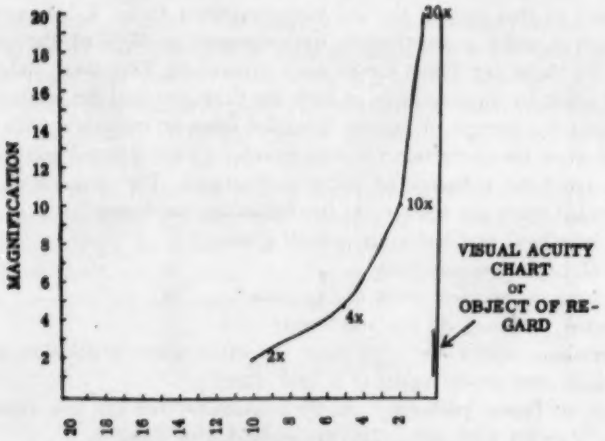
* Lenses were prescribed for 271 patients, but it was only possible to evaluate 240, because some never had their prescriptions filled and others failed to return for evaluation.

The classification as presented is greatly oversimplified, because 50% of the patients presented themselves with multiple ocular pathology, e.g., corneal opacities, cataracts, and glaucoma.

Some types of pathology impressed the examiner as offering a more favorable prognosis than others. Albinism, postoperative aphakia, myopic chorioretinal degeneration, and macular degeneration seem to be the most promising, whereas retinitis pigmentosa, diabetic retinopathy, and glaucoma are the least promising. While the percentage of success is not too significant in so few cases, an indication of the pathology favorable for correction is made. The fact that albinos and patients with postoperative aphakia due to removal of congenital cataracts are promising and that those with retinitis pigmentosa and glaucoma are least promising is supported by my experience in my private practice. Patients whose visual fields are greatly constricted seem to have a poor prognosis for a successful correction.



MAGNIFICATION INCREASES INVERSELY AS DISTANCE FROM OBJECT IS REDUCED.

The Figure demonstrates nonoptical magnification for distant and near vision. Using the abscissa expressed in feet, one can readily interpret the magnification produced by moving up to the object of regard. This explains the fact that patients with 5/200 vision enjoy television by sitting 2 ft. from the screen, which gives them 10 × magnification.

If one applies the abscissa expressed in inches, this diagram shows the magnification gained by bringing the reading matter close to the eyes. This explains the fact that young patients who are not aphakic and myopic paients can read textbooks at distances of 3 to 4 in. from their eyes when their distant vision is 20/200 or less.

The diagram also demonstrates the magnification produced by strong plus lenses, because the lenses enable the patient to read print at close range, thereby producing greater magnification. Print that subtends an over-all visual angle of 5 minutes at 20 in. (considered nomal vision when read at 20 in.) is magnified 10 times when read at 2 in. from the eye. This can be accomplished by an adult wearing a +40.00 D. sphere.

The types of lenses prescribed were classified as regular, simple magnifying, doublet magnifying, microscopic bifocals, contact, and telescopic, as shown in Table 2. The vision of 58 patients was improved by regular lens correction: E.g.,

TABLE 2.—*Type of Correction and Results*

Type of Lenses	Number Prescribed	Number Successful	Percentage Successful
Regular	56	41	73
Magnification	138	94	68
Doublet	31	26	84
Microscopic bifocal	7	6	86
Contact	7	5	71
Telescopic	1	1	

an albino who was wearing no glasses was greatly benefited by the following correction: O. D.−8.50 sph⌒+1.00 cyl, ax 90; O. S.−1100 sph⌒+1.75 cyl, ax 90. There were a few aphakic patients examined who had been wearing no correction; consequently they appreciated the usual strong plus correction. These were a group of patients who required only a correct refraction.

One hundred thirty-eight patients were given prescriptions for simple magnifying lenses. These can be considered simple microscopic lenses. These corrections ranged from +8.00 D. sphere to +36.00 D. sphere. Many of the strong plus corrections were given in the form of bifocals when the distant correction improved distant vision. The strongest addition prescribed in a bifocal was +36.00 D.

Half-eye magnifying glasses proved most useful for patients requiring no significant distant correction.

Doublet magnifiers, also known as microscopic type or clear-image lenses, were prescribed for 31 patients. The powers ranged from 8 × magnification to 20 × magnification. The high percentage of favorable results was impressive with the 8 × and 12× magnifications.

The microscopic bifocal consisting of a Hastings triplet cemented into a plastic lens was prescribed for seven patients. Gratifying results were obtained by the 10 × magnification and 14 × magnification.

Contact lenses were prescribed for seven patients. The ocular pathology responsible for the low vision was corneal in five patients and chorioretinal degeneration due to high myopia in two patients. The contact lenses were prescribed by Allan Rossby, M.D., of New York City, who has been actively engaged in this field for the past 14 years.

One pair of 2.2 × magnification telescopic spectacles with a +8.00 reading addition was prescribed. That only one pair of telescopic spectacles was prescribed for 1 of 240 patients for whom low-vision corrections were fitted may be as startling to the reader as it was to the examiner. A greater demand for telescopic spectacles had been anticipated, owing to the prevalence of television. The majority of patients with low vision enjoyed television and could look at it for hours by sitting at distances ranging from 1 to 3 ft. from the screen. Those who owned telescopic lenses preferred to sit closer to the screen and not wear the lenses. The examiner believed that there were no patients in this group whose near vision would be benefited more by telescopic lenses than by a simple magnifying lens. The one patient for whom a telescopic spectacle was prescribed could read print smaller than Jaeger 1 at 60 mm. from his left eye with no lens correction.

The distant correction was — 18.00 sph ⊃+3.50 cyl, ax 90 = vision 20/200. However, one patient, a shoemaker, was examined who was wearing telescopic lenses at his work. In such a case no other magnifying device would supplant the telescopic lenses, because a maximum working distance is essential for this trade. In 10 patients telescopic lenses were replaced by other magnifying devices; bifocals with strong reading additions in four cases, strong plus lenses in four cases, and 12 × magnification doublet lenses in two cases. These lenses were found preferable to the telescopic lenses by all 10 patients, as evidenced by the fact that the telescopic spectacles were no longer worn.

It is instructive to note that regular lenses and simple magnifying lenses were prescribed in 81% of cases.

TABLE 3.—*Visual Acuity and Results*

Range of Visual Acuity	Number	Number Successful	Percentage Successful
1/200	1		
3/200-10/200	94	72	77
11/200-20/200	64	48	75
20/180-20/100	55	36	65
20/80-20/50	20	12	60
20/40-20/20	6	5	83

Table 3 records the degree of visual defect encountered in this project as well as the number in each group and the incidence of successful cases. It shows that 66% of the patients having low vision seeking correction have a visual acuity of 20/200 or less. Successful corrections were obtained in 76% of this group. Of the six patients whose vision ranged from 20/40 to 20/20, five suffered from advanced chronic simple glaucoma with markedly constricted fields.

The ages of the patients for whom low-vision lenses were prescribed ranged from 6 years to 98 years. Table 4 shows the number of lenses prescribed according to age incidence.

TABLE 4.—*Age Incidence of Patients for Whom Low-Vision Lenses Were Prescribed*

Age Range, Yr.	Cases, No.
0-20	22
21-40	51
41-60	91
61-98	46

Summary and Conclusions

Of 500 patients with low vision the examiner believed that 240 patients could be partially rehabilitated with low-vision lenses.

Of the 240 cases in which lenses were prescribed, 72% were considered successful by the patient and the examiner.

Relative frequency of ocular pathology responsible for low vision is enumerated.

Types of lenses prescribed, the number of each kind, and the percentage of successful results are tabulated.

Degree of visual defect, incidence, and percentage of successfully corrected cases are tabulated.

Vision can be corrected in 81% of patients with low vision by a careful refraction or by the use of strong plus lenses.

There seems to be a small need for telescopic spectacles, especially for distant use.

Ten patients who had been wearing telescopic lenses for reading were fitted with bifocals with strong reading additions or strong plus lenses or doublet magnifiers, which they found preferable to telescopic lenses.

Eighty-four per cent of the doublet magnifiers were successful.

Eighty-six per cent of the microscopic bifocals were successful.

Seventy-one per cent of contact lenses were successful.

Mr. Conrad Carlsen, of Haustetter & Company, dispensed the lenses used in this project.

Miss Ann Marcus performed various services in many capacities for the efficient operation of the Low Vision Service at the Lighthouse.

Hazards of the Use of Sympathomimetic Drugs in Ophthalmology

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Sympathomimetic drugs such as epinephrine (Adrenalin), phenylephrine (Neo-Synephrine), and hydroxyamphetamine (Paredrine) have attained widespread popularity among ophthalmologists. Their effects of mydriasis and vasoconstriction are useful in refraction, in ophthalmoscopic examination, in the therapy of conjunctivitis and of uveitis, and in control of surgical bleeding. Also, because of their prolonged hypotensive effect, sympathomimetic-miotic combinations have been used in the therapy of wide-angle glaucoma.

Thus, the importance of the sympathomimetic drugs, both diagnostically and therapeutically, is well recognized. However, ophthalmologists generally regard this important group of drugs as harmless, except for the possibility of precipitating acute narrow-angle glaucoma. We, therefore, feel it worth while to present a case of acute subarachnoid hemorrhage resulting from the use of phenylephrine and to discuss other reported hazards of the sympathomimetic drugs.

Report of a Case

A 35-year-old white man had been treated two weeks for an acute iritis O. S. by one of us (J. W.H.). Despite local 1% atropine sulfate drops given hourly and intravenous typhoid H antigen therapy, posterior synechiae had formed. An attempt was made to break the synechiae by placing a cotton wick soaked with 10% phenylephrine hydrochloride solution in the lower conjunctival cul-de-sac. After a few minutes the patient suddenly complained of a severe occipital headache, which he described as intensely throbbing in character. His blood pressure was taken and found to be 230/130, although on previous examinations it had been 118/68. The cotton wick was removed immediately.

The headache continued, and the patient began to note pain and stiffness in the cervical and lumbar regions. He was admitted to the University of Michigan Hospital for neurologic observation. Examination disclosed nuchal rigidity and Kernig's sign as evidence of meningeal irritation, but there were no localizing findings. A mild febrile reaction was noted for the first three days after admission, and the blood pressure remained approximately 120/80. Lumbar puncture showed uniformly bloody spinal fluid with a pressure of 200 mm. of water. The supernatant fluid, after centrifugation, was xanthochromic and contained 120,000 red blood cells and 1280 white blood cells per cubic millimeter. Skull films and visual

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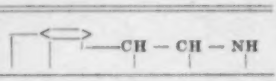
fields were normal. Arteriography was not performed. A diagnosis of subarachnoid hemorrhage was made and the patient was kept at bed rest.

Two weeks later a lumbar puncture yielded clear slightly yellow fluid with a pressure of 140 mm., 38 red blood cells and 1 white blood cell per cubic millimeter, 85 mg. of protein per 100 cc., negative gold and mastic curves, and a negative Kahn reaction. During hospitalization of one month all symptoms disappeared. The patient has experienced no further neurologic difficulties in the past six years.

Comment

The most commonly used sympathomimetic agents in ophthalmology are shown in the Table. As expected from their related formulas, the physiologic actions

Formulas of Commonly Used Sympathomimetic Drugs

					
			—CH — CH — NH		
Epinephrine (Adrenalin)	OH	OH	OH	H	CH_3
Phenylephrine (Neo-Synephrine)	H	OH	OH	H	CH_3
Ephedrine	H	H	OH	CH_3	CH_3
Hydroxyamphetamine (Paredrine)	OH	H	H	CH_3	H

of these drugs are similar in many respects. The main differences lie in duration and in intensity of action. For example phenylephrine, like epinephrine, can produce a pronounced vasopressor action, but of less intensity and of longer duration. Ephedrine and paredrine have only 1/100 the pressor activity of epinephrine, but a longer duration of action.

Drill[1] discusses three types of toxic effects which may follow overdosage or inadvertent intravenous injection of these drugs. First, cerebral vascular accidents may result from increased arterial pressure. Second, because of cardiac stimulation and peripheral constriction, pulmonary edema from pulmonary arterial hypertension may be the fatal toxic response. A third cause of death may be ventricular hyperirritability. Epinephrine may cause ventricular fibrillation if used in patients who are receiving chloroform or cyclopropane anesthesia or who have had excessive doses of digitalis or mercurial diuretics. Ephedrine and paredrine, like epinephrine, are capable of producing disturbances of cardiac rhythm but do so much less frequently. Phenylephrine differs from epinephrine in that it does not cause cardiac stimulation or fibrillation with cyclopropane.

The usual therapeutic doses of the sympathomimetic drugs not infrequently produce minor toxic effects such as anxiety, tremor, headache, and palpitation. These generally result when epinephrine has been employed as a vasoconstrictor to prolong local anesthesia, and the effects are transient and not dangerous. Should a marked rise in blood pressure be noted, vasodilators such as nitrites may be employed. Barbiturates may be necessary for central sedation. Epinephrine should not be used in cases of hyperthyroidism, angina pectoris, or cardiac

dilatation, because of the possibility of hypersensitivity. Phenylephrine, because it produces less central and cardiac effects, may be substituted with care. For combination with local anesthetics, a solution of 1:5000 phenylephrine is adequate.

As previously mentioned, the most serious toxic effects generally follow large dosage of intravenous use of the sympathomimetics. However, Keeney [2] reported a case of hemiplegia in a 33-year-old man following the subcutaneous injection of only 0.5 cc. of 1:1000 epinephrine. After a similar injection subarachnoid hemorrhage occurred in a 20-year-old woman described by Flexner and Schneider.[3] No report similar to our case of subarachnoid hemorrhage following phenylephrine could be found. However, the possibility of such toxicity has been considered.

Heath [4] in 1936 first described the uses of phenylephrine in ophthalmology and noted that the drug when applied to a dog cornea in powder form caused an abrupt and pronounced rise in blood pressure. He warned, therefore, that some care was needed in the use of the pure drug in patients with arteriosclerosis and hypertension. Schepens [5] noted clinically that the pure drug applied to the cornea "may cause unpleasant systemic reactions such as nervousness, pounding of the heart, violent occipital headaches, nausea, and vomiting." In 1949, Heath and Geiter [6] reported that they had never noted any harmful effects from phenylephrine. They acknowledged that rapid absorption of substantial amounts of the drug "causes marked and hazardous increase of the blood pressure" but added that "systemic absorption through the anterior segment of the eye is slow and limited in degree." To study this, they measured the blood pressure of 120 patients before and after the topical instillation of phenylephrine and found no increase in blood pressure in 98% of patients and only a slight increase in 2%.

To substantiate the above study and to determine whether hypertensive patients were more sensitive, we instilled 10% aqueous phenylephrine in a series of 100 hypertensive patients. The blood pressure was recorded before and after instillation. No elevation was found in 94. Six showed elevations of pressure no greater than 10 mm. Hg. Since greater systemic absorption would be expected through an open wound, the effects of topical epinephrine and phenylephrine were observed in 20 cases undergoing strabismus surgery. Here, again, no elevation of blood pressure in excess of 10 mm. Hg was observed. Such an elevation could scarcely be regarded as dangerous.

In the case of subarachnoid hemorrhage described, there exists the possibility that systemic absorption of the topical atropine had a vagal blocking effect which permitted exaggerated response to the phenylephrine. This type of response, however, was not noted in the above strabismus cases, all of whom had atropine as preoperative medication. However, if the cumulative dosage of 1% atropine sulfate drops given hourly is considered, a direct comparison is not easy. Certainly it would seem wise to avoid the use of the more potent sympathomimetics if vagal blocking exists.

Summary

The sympathomimetic drugs such as epinephrine (Adrenalin), phenylephrine (Neo-Synephrine), and hydroxyamphetamine (Paredrine) are widely used in ophthalmology and generally regarded as harmless.

Minor toxic effects may include anxiety, tremor, palpitation, and headache. These are transient and not dangerous.

Potential major toxic effects are subarachnoid hemorrhage, ventricular fibrillation, or acute pulmonary edema.

A case of subarchnoid hemorrhage in a 35-year-old man following the use of a cotton wick soaked with 10% phenylephrine solution is reported.

Fortunately, the sympathomimetic drugs have a wide margin of safety, and such serious toxic effects are very rare. One hundred hypertensive patients were studied, and no significant systemic reactions to 10% aqueous phenylephrine were noted. Nevertheless, these drugs should not be used indiscriminately, and certain contraindications are discussed.

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Hypersecretion Glaucoma

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Clinical tonography has added greatly to our understanding of the pathogenesis of chronic simple (open angle) glaucoma. There has been adequate confirmation of the initial conclusion of Grant [1] that "increase in intraocular pressure in glaucoma is practically always, possibly exclusively, caused by increased resistance to outflow of aqueous humor from the eye (i.e., subnormal facility of outflow), and not by hyperformation of the aqueous humor." However, with the increased use of repeated tonography the rare exceptions to this thesis appeared. Thus, Becker and Friedenwald,[2] in reviewing 1500 tonograms on 250 consecutive patients, noted 5 subjects who had repeated tracings demonstrating elevated tensions without impaired facility of outflow. These eyes were demonstrated to have normal values for corneal curvature and scleral rigidity. Ballintine [3] also noted a few patients with chronic simple glaucoma and elevated intraocular pressure but with normal facilities and normal scleral rigidities.

With use of the 1955 tables of Jonas S. Friedenwald,[4] normal values for facility outflow (C) in our laboratory vary from 0.20 to 0.60, with a mean of 0.33. Flow (F), values for normal and glaucomatous eyes average 2.3 cu. mm. per minute when calculated from the following formula:

$$F = (P_o - 10) \times C$$

where

P_o = intraocular pressure.

For purposes of this investigation, hypersecretion was arbitrarily defined as flow greater than 4.0 cu. mm/minute when calculated by the above formula. Only patients with a facility of 0.20 or more, when their intraocular pressure was elevated, were included in the present series. A review of more than 7500 tracings on 1300 consecutive persons referred for tonography revealed 128 eyes of 65 patients with findings of apparent increased intraocular pressure and normal facility of outflow, open angles, and no ocular surgery or evidence of inflammatory diseases. It was the purpose of this investigation to evaluate the significance of such tonographic findings.

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Methods

Of the 65 patients who demonstrated this rare finding, it was possible to re-examine 60 (118 eyes). All such patients had repeated tonograms (10 to 40 tracings per patient) over a period of six months to two years. In each instance measurements of scleral rigidity were carried out (5.5 vs. 10 gm. weights). All tensions and tonograms were performed with a Mueller electronic tonometer attached to a Leeds & Northrup recorder. Repeated central and peripheral visual fields were charted as well as gonioscopic and ophthalmoscopic examinations. Water-drinking provocative tests were carried out on 19 of these patients while they were not receiving any therapy and after a nine-hour fast. Tonography was performed prior to the consumption of 1 liter of water and one hour after.

Results

Of the 118 eyes that met the criteria of open angles and apparent flow greater than 4 cu. mm/min., 30 eyes of 15 patients could be eliminated from the hypersecretion group because of high scleral rigidity (Table 1). It is of interest

TABLE 1.—*Scleral Rigidity in Eyes with Apparent Increased Secretion*

	Eyes		Patients	
	No.	%	No.	%
Increased rigidity	30	25	15	25
Normal rigidity	88	75	45	75
Total	118		60	

in this group of 15 patients that, when appropriate corrections were applied for the elevated scleral rigidity, flow was truly normal. Sixteen of the thirty eyes with increased scleral rigidity had corrected values for facility of outflow (C) that were decreased to glaucoma levels. Ten of these sixteen eyes had glaucomatous field loss. Fourteen eyes of seven patients were found to have normal values for intraocular pressure (P_o) and facility (C) when correction was made for high scleral rigidity. None of these eyes had evidences of field loss. Such eyes were apparently entirely normal, and these instances merely represented errors

TABLE 2.—*Visual Field Loss in Eyes with Increased Scleral Rigidity*

	Eyes, No.	Field Loss (Eyes)	Patients, No.	Field Loss Patients
Decreased facility	16	10 (63%)	8	7 (88%)
Normal facility	14	0	7	0
Total	30	10	15	7

in the methods of measurement induced by high scleral rigidity (Table 2).

There were 88 eyes of 45 patients which demonstrated hypersecretion, normal scleral rigidity, and open angles. Values of facility (C) in these eyes varied from 0.20 to 0.60 and averaged 0.33, values very similar to the average and range for normal eyes in this laboratory. Intraocular pressure (P_o) in this group varied from 20 mm. Hg to 45 mm. Hg and averaged 27 mm. Hg on repeated tonograms. (The average for normal eyes in this laboratory is 17 mm. Hg.)

Most of the patients (78%) demonstrated variable rates of flow with intermittent hypersecretion. However, in every instance, when the intraocular pressure was borderline or elevated, facility of outflow was not decreased. Flow rates for the eyes in this series during phases of hypersecretion varied from 4 to 10 cu. mm/min., with a mean of 5.7 cu. mm/min. (as compared with a mean of 2.3 cu. mm/min. for normal eyes).

Of the 88 eyes classified as having hypersecretion glaucoma, 50 (57%) demonstrated some field loss (Table 3). More significantly, this occurred in

TABLE 3.—*Visual Field Loss in Hypersecretion Glaucoma*

	Eyes, No.	Field Loss (Eyes)		Patients, No.	Field Loss (Patients)	
		No.	%		No.	%
Persistent hypersecretion	19	19	100	10	10	100
Intermittent hypersecretion	69	31	45	35	18	51
Total	88	50	57	45	28	62

28 (62%) of the 45 patients of this group. One may classify field loss arbitrarily as follows:

0 = no field loss
1 + = pathological enlargement of the blind spot
2 + = arcuate scotoma and/or early nasal field loss
3 + = advanced nasal field loss and arcuate scotomata

On this basis, in this series 5 eyes were found to have 3+ field loss: 9 eyes, 2+, and 36 eyes, 1 +. It is of interest that degree of field loss tended to correlate with the mean value for intraocular pressure (Table 4). Thus, those eyes

TABLE 4.—*Relation of Field Loss to Intraocular Pressure (P_0) and Facility (C) in Hypersecretion Glaucoma*

Field Loss	Eyes, No.	Mean P_0, Mm. Hg	Mean C
0	38	24	0.35
+	36	28	0.32
++	9	31	0.31
+++	5	37	0.25

with 3+ field loss had intraocular pressure averaging 37 mm. Hg; those with 2+ field loss averaged 31 mm. Hg; the 36 eyes with 1+ field loss averaged 28 mm. Hg, and the 38 eyes with no field loss averaged 24 mm. Hg. Facility of outflow averaged 0.35 in those that lost no field, 0.32 in those with 1+ field loss, 0.31 for the 2 + field loss group, and 0.25 in the five eyes with marked field loss. Furthermore, the 19 eyes with persistent hypersecretion tended to lose field more consistently and to a greater degree than the 69 with intermittent and variable hypersecretion (Table 3).

Water-drinking provocative tests were carried out on 19 patients of the series of hypersecretors. Of the 37 eyes, 13 (35%) had a pressure rise of 8 mm. Hg or greater (Table 5). In contrast to the frequently induced decrease in facility noted in most eyes with chronic simple glaucoma and positive water provocative tests, the rise in intraocular pressure in this series resulted from

TABLE 5.—*Water-Drinking Provocative Tests in Hypersecretion Glaucoma*

Pt. No.	Eye	Before H_2O			After H_2O		
		P_o*	C†	F	P_o	C	F
2	OD‡	27	0.30	5.4	42	0.22	7.0
	OS‡	22	0.44	5.3	30	0.30	6.0
8	OD	21	0.24	2.6	27	0.30	5.4
	OS	19	0.26	2.3	21	0.30	3.3
9	OS‡	17	0.25	1.8	27	0.44	7.5
10	OD	29	0.30	5.7	35	0.42	10.5
	OS	30	0.32	6.4	29	0.50	9.5
14	OD	32	0.30	6.6	30	0.52	13.5
	OS	32	0.30	6.6	35	0.55	13.8
15	OD	24	0.35	4.9	25	0.54	8.1
	OS	17	0.40	2.8	21	0.54	5.9
21	OD	23	0.33	4.3	27	0.39	6.6
	OS	23	0.35	4.6	26	0.45	7.2
22	OD	16	0.41	2.5	20	0.37	3.7
	OS	15	0.40	2.0	19	0.42	3.8
23	OD	21	0.21	2.3	24	0.27	3.8
	OS‡	24	0.20	2.8	32	0.38	8.4
24	OD	21	0.20	2.2	28	0.27	4.9
	OS‡	24	0.20	2.8	35	0.32	8.0
25	OD	24	0.49	6.9	27	0.49	7.3
	OS	22	0.55	6.6	25	0.59	8.9
29	OD‡	18	0.22	1.8	30	0.35	7.0
	OS‡	17	0.24	1.7	29	0.30	5.7
31	OD‡	22	0.20	2.4	32	0.27	5.9
	OS‡	21	0.20	2.2	32	0.27	5.9
33	OD	22	0.40	4.8	24	0.44	6.2
	OS	21	0.35	3.8	22	0.40	4.8
34	OD‡	24	0.35	4.9	32	0.48	10.6
	OS‡	22	0.33	4.0	30	0.44	8.8
35	OD	19	0.35	3.2	24	0.40	5.6
	OS	21	0.37	4.1	24	0.40	5.6
41	OD	27	0.39	6.6	28	0.41	7.4
	OS	27	0.39	6.6	30	0.56	11.0
42	OD	29	0.24	4.6	32	0.27	6.0
	OS	29	0.24	4.6	30	0.30	6.0
44	OD‡	24	0.25	3.5	36	0.32	8.3
	OS‡	19	0.20	1.8	29	0.30	5.7

* P_o, intraocular pressure (mm. Hg).
† C, facility of outflow.
‡ Significant rise in intraocular pressure (8 mm. Hg or more).

increased secretion in all instances. In fact, in only 1 patient of the 19 subjected to water administration were significant decreases in *C* noted following water-drinking. On the other hand, in a large series of untreated chronic simple glaucoma, over 90% of eyes responded to water-drinking with a decrease in facility of outflow.[5]

It was repeatedly noted that almost all patients with hypersecretion glaucoma tended to be "high strung," emotionally labile persons, frequently with neurogenic hypertension. A compilation of the pertinent average data on each of the 45 patients of the hypersecretion series is presented in Table 6. Values obtained under the influence of acetazoleamide or other carbonic anhydrase inhibitors are not included, however. An abstract of the histories of two representative patients of this series serves to illustrate the syndrome.

Report of Cases

CASE 37.—A 48-year-old factory foreman was found to have elevation of intraocular pressure during a routine examination for glasses. He was referred for study in March, 1954. He had noted no ocular symptomatology. Examination revealed 20/15 vision in both eyes, open angles, normal depth of anterior chamber, and no evidence of inflammatory disease. He had early hypertensive retinopathy, but there was no cupping or atrophy of the nerve heads. Tension measured 32 mm. Hg, R. E., and 34 mm. Hg, L. E., and the scleral rigidity was normal. Peripheral and central visual fields were found to be full. Tonography: R. E., $P_o = 32$ mm. Hg, $C = 0.28$; L. E., $P_o = 34$ mm. Hg, $C = 0.27$. A medical check-up revealed neurogenic hypertension of six years' duration.

The patient was noted to be emotionally labile, and blood pressure readings were variable.

He was placed on a regimen of pilocarpine 2% four times daily. Intraocular pressures remained in the high 20's and low 30's, but always with normal facilities. In September, 1954, a tonogram while he was using pilocarpine revealed the following: R. E., P_o=40 mm. Hg, C=0.25; L. E., P_o=42 mm. Hg, C=0.22, with normal scleral rigidities. An early arcuate scotoma to 1/1000 white was recorded in each eye at that time. Therefore, the patient was placed on acetazoleamide therapy, 250 mg. every six hours, in addition to continuing his miotic therapy. On this regimen the intraocular pressure was maintained in the low

TABLE 6.—*Hypersecretion Glaucoma: Data on Eighty-Eight Eyes of Forty-Five Patients*

Intermittent Hypersecretion (69 eyes of 35 patients) No.	Age	Race	Sex	Eye	Mean P_o,* Mm.Hg	Mean C†	Field Loss‡
1	55	W	F	OD	34	0.33	+
				OS	34	0.31	+
2	55	N	F	OD	32	0.30	+
				OS	32	0.33	+
3	50	N	F	OD	30	0.50	+
				OS	30	0.50	+
4	55	W	F	OD	30	0.30	+
				OS	30	0.33	+
5	55	W	M	OD	29	0.25	+
				OS	30	0.25	+
6	55	W	F	OD	30	0.28	+
				OS	25	0.30	0
7	49	W	M	OD	28	0.33	0
				OS	28	0.35	0
8	50	N	M	OD	28	0.30	0
				OS	28	0.30	0
9	53	W	F	OS	28	0.35	0
10	53	N	F	OD	28	0.30	+
				OS	28	0.32	+
11	43	W	F	OD	28	0.30	+
				OS	28	0.30	+
12	51	W	M	OD	24	0.39	0
				OS	28	0.33	+
13	75	W	F	OD	27	0.31	+
				OS	27	0.34	+
14	43	W	M	OD	27	0.30	0
				OS	27	0.30	0
15	51	W	M	OD	27	0.30	++
				OS	25	0.33	++
16	55	W	F	OD	26	0.33	0
				OS	26	0.35	0
17	55	N	M	OD	26	0.29	0
				OS	26	0.27	0
18	78	W	F	OD	26	0.40	+
				OS	26	0.38	+
19	69	W	M	OD	20	0.40	0
				OS	26	0.25	++
20	50	W	F	OD	25	0.30	0
				OS	25	0.30	0
21	55	W	F	OD	25	0.33	0
				OS	25	0.35	0
22	67	W	F	OD	25	0.33	0
				OS	25	0.31	0
23	65	W	F	OD	25	0.30	0
				OS	25	0.31	0
24	56	W	F	OD	25	0.36	0
				OS	25	0.35	0
25	51	W	M	OD	25	0.49	0
				OS	23	0.55	0
26	38	W	M	OD	25	0.38	+
				OS	20	0.45	0
27	52	W	M	OD	24	0.25	+
				OS	24	0.26	+
28	75	W	F	OD	24	0.40	+
				OS	24	0.42	+
29	63	W	F	OD	24	0.30	+
				OS	24	0.30	+
30	27	W	F	OD	24	0.55	0
				OS	24	0.55	0
31	51	W	F	OD	23	0.25	0
				OS	22	0.25	0
32	47	W	F	OD	22	0.38	0
				OS	22	0.37	0
33	50	N	F	OD	22	0.40	+
				OS	21	0.35	0
34	52	W	M	OD	22	0.30	0
				OS	22	0.34	0
35	57	W	M	OD	20	0.37	0
				OS	22	0.38	0

TABLE 6.—*Hypersecretion Glaucoma: Data on Eighty-Eight Eyes of Forty-Five Patients (Continued)*

No.	Age	Race	Sex	Eye	Mean P_o,* Mm.Hg	Mean C†	Field Loss‡
Persistent Hypersecretion (19 eyes of 10 patients)							
36	80	W	F	OD	40	0.28	+++
				OS	40	0.28	+++
37	48	W	M	OD	35	0.35	++
				OS	35	0.35	++
38	55	N	F	OD	35	0.30	++
				OS	35	0.20	+++
39	65	W	F	OD	35	0.25	+++
				OS	35	0.25	+++
40	67	W	F	OD	30	0.30	+
				OS	34	0.20	++
41	72	W	M	OD	30	0.35	++
				OS	30	0.35	++
42	55	W	F	OD	30	0.24	+
				OS	30	0.24	+
43	65	W	M	OS	28	0.26	+
44	52	W	F	OD	28	0.24	+
				OS	28	0.24	+
45	65	W	F	OD	26	0.28	+
				OS	26	0.28	+

* P_o, intraocular pressure (mm. Hg).
† C, facility of outflow.
‡ O, no field loss;
+, pathological enlargement of the blind spot and/or baring of the blind spot;
++, arcuate scotoma and/or early nasal field loss;
+++, advanced nasal field loss and arcuate scotomata.

20's in both eyes. Tonography in November, 1954: R E, P_o=22 mm. Hg, C=0.22; L. E., P_o=21 mm. Hg, C=0.24. Repeat tonography in December, 1954, and January, February, May, August, September, and October, 1955, revealed variations of intraocular pressure in the range of 19 to 24 in each eye, with facilities of 0.20 to 0.30. There was no further progression of field loss to the time of his death, from a myocardial infarction, in December, 1955. Both eyes were obtained at autopsy and are in the process of serial section. Facilities of outflow determined by perfusion of the enucleated eyes six hours after death were R. E., 0.30; L. E., 0.28.

CASE 4.—A 55-year-old housewife was found to have elevated intraocular pressure in both eyes in 1946 and had been treated with miotics. In spite of pilocarpine 4% four times daily, tensions remained elevated. She was referred for evaluation in October, 1954. There was no history of pain, inflammation, or halo vision. She had known intermittent systemis hypertension since 1951. Vision: R. E., 20/25; L. E., 20/20—1. Examination revealed no external abnormalities, deep anterior chambers with open angles, and no evidence of inflammatory disease. The fundi were normal except for early cupping of the discs. Tonography: R. E., P_o=35 mm. Hg, C=0.35; L. E., P_o=35 mm. Hg, C=0.37. Scleral rigidity was normal. Central fields revealed bilateral enlargement of blind spots to 1/1000 white test object. Repeat tonograms revealed pressures in the range of 28 to 32 mm. Hg, with facilities of 0.30 to 0.35. The patient was placed on acetazoleamide, 250 mg. every six hours, in October, 1954. Intraocular pressures and repeated tonograms during 1954 and 1955 varied from 19 to 22 mm. Hg, with facilities of 0.30 to 0.35. No further field loss was noted as of March, 1956 (17 months on acetazoleamide).

Therapy

In reviewing the histories of hypersecretors it becomes apparent that treatment has offered considerable difficulty in this group of patients in the past. Although miotics or filtering operations may lower intraocular pressure for a time in some of these eyes, they appear to do so by a depression of flow rather than by a further improvement in the facility of outflow. Tension control

following such therapy has usually been inadequate, and field has been lost progressively, but usually very slowly (especially in the intermittent hypersecretion group). The recent availability of agents which induce partial suppression of aqueous secretion appears to offer the best opportunity for lowering intraocular pressure over any period. It has been our experience that therapy with acetazoleamide or other carbonic anhydrase inhibitors has prevented further field loss and tended to buffer the episodes of hypersecretion. In several persons sedation or tranquilizing agents (e.g., chlorpromazine or Rauwolfia alkaloids) have been of some benefit in this group of glaucoma patients.

Discussion

In a consideration of the incidence of hypersecretion glaucoma, it should be emphasized that the series of some 7500 tonograms reviewed were all of patients referred to a tonography laboratory for diagnosis or evaluation of therapy. In such a group of 1300 consecutive patients, 65 (5%) presented a type of tracing with apparent elevated tension and normal or high facility. Of the 60 of these patients who could be examined extensively, correction for abnormal scleral rigidity eliminated 15 (25%) from the hypersecretion group. This would place the incidence of true hypersecretion glaucoma in such a referred group of patients at less than 4%. This figure is undoubtedly too high even for such a series of patients, however, because once the syndrome had been defined there was an increased incidence of referred hypersecretion suspects. The incidence of hypersecretion in a large clinic population of glaucoma patients appears to be less than 2%. On the other hand, if one limits the present tonographic series to eyes not operated on, with open angles and no evidence of inflammatory, vascular, or neoplastic diseases, the incidence of hypersecretion glaucoma in this highly selected group rises to about 8%. Furthermore, in a series of 50 selected private patients over the age of 40 years, referred from one ophthalmologist's office for borderline tensions in the absence of signs or symptoms of glaucoma, 4 (8%) proved to have hypersecretion glaucoma.[6] It may be concluded that this is a rare form of glaucoma except in selected series.

The findings in the increased rigidity series of 30 eyes are of interest. They revealed that some eyes with increased rigidity are truly nonglaucomatous and others have glaucoma. This is by no means the over-all incidence of high scleral rigidity, but merely includes those patients with sufficiently elevated scleral rigidity to simulate hypersecretion glaucoma as arbitrarily defined here, as to both apparent facility and apparent intraocular pressure. Increased scleral rigidity is one of the major considerations in differential diagnosis of hypersecretion glaucoma.

It is evident that the diagnosis of hypersecretion glaucoma involves the use of repeated tonograms with corrections for scleral rigidity. The initial reluctance to label these patients as having glaucoma in the face of normal or even high-normal facility of outflow has been overcome in recent years because of the findings of progressive field loss in such eyes. The high incidence of field loss received in this series (57% of eyes and 62% of patients) is undoubtedly related to the type of cases referred to a tonography laboratory. Intermittent hypersecretors are probably often misdiagnosed in office practice, even by tonography, if seen during a normal phase. On the other hand, the eyes that lose field are subjected to a more intensive investigation.

It is quite apparent that the hypersecretion syndrome is not independent of facility of outflow, for, although the major cause of the increase in intraocular pressure in these eyes appears to be a persistent or intermittent hypersecretion of aqueous humor, the extent of the elevation of intraocular pressure for a given increase in secretory rate is dependent upon the facility of outflow. Perhaps the ability of the eye to compensate for its increased rate of secretion by increasing its outflow facility may determine rapidity of field loss.

It is important to reemphasize the rarity of the occurrence of hypersecretion glaucoma even in large glaucoma populations. It is hoped that the separation of this unusual group of open-angle glaucomas from the more conventional variety will permit a more careful study of the mechanisms involved in the phenomenon of hypersecretion. It may also serve to delineate more sharply the residual larger group of open-angle glaucoma with impaired outflow. Thus, the hypersecretors account for a part of the bothersome overlap of the normal glaucoma population in regard to facility of outflow. It is further apparent that the response to water-drinking provocative tests is quite different in the two groups. Of practical significance is the suggestion that therapy in the hypersecretion group must be directed toward suppression of secretion and that little can be accomplished by efforts at further increasing facility of outflow. This is, of course, in sharp contrast to the more usual forms of open-angle glaucoma, where miotics and improvement of outflow facility are the most dramatic and important forms of treatment.

Summary

Forty-five patients with hypersecretion glaucoma are reported. This rare, but distinct, entity is characterized by intermittent or persistent elevations of intraocular pressure in the absence of disordered outflow facility. It must be differentiated from increased scleral rigidity. Hypersecretion glaucoma results in field loss, the extent of which appears to depend upon the degree of elevation of intraocular pressure. It responds more favorably to partial suppression of secretion by such methods as acetazoleamide administration than it does to more conventional miotic or surgical therapy.

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Dissimilarity of Retinal Microaneurysm and Glomerular Nodule in Diabetes

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There are two distinct and specific vascular lesions associated with diabetes mellitus in man, the retinal capillary microaneurysm and the glomerular nodule. The two may be found concomitantly in many diabetics, and some investigators have assumed these lesions to be similar. I feel that the retinal capillary microaneurysm, found almost exclusively in diabetes mellitus, is quite different from the specific nodule of intercapillary glomerulosclerosis. Both lesions have thus far been found only in man, and neither has been reliably produced in experimental animals.*

This paper attempts to clarify the relationship between the specific retinal and renal lesions with regard to chronology, pathogenesis, and specificity.

Diabetic Retinopathy

The ophthalmoscopic appearance of diabetic retinopathy is variable (Fig. 1).

One of the earliest signs, if not the earliest sign, of diabetic retinopathy is the appearance of ophthalmoscopically visible capillary microaneurysms and punctate hemorrhages. These are located in the inner nuclear and outer plexiform layers of the retina. Concomitantly or later, sharply demarcated exudates, consisting of lipohyalin, are found in the deep layers of the retina. The lesions are found predominantly in the macular area. Dilation of the retinal venules and veins is also characteristic of the disease. The above findings in combination are unique for diabetes mellitus. The lesion which is specific, however, is the characteristic capillary microaneurysm, which is seen almost exclusively in diabetes, and it alone will enable the ophthalmologist to make an accurate diagnosis.

In later stages, small and large retinal hemorrhages appear. The development of new vessels within the retina and vitreous body and the formation of fibrous connective tissue comprise the picture known as retinitis proliferans.

The Retinal Capillary Microaneurysm

The specific characteristic retinal lesion is the retinal capillary microaneurysm, varying from 20μ to 100μ in diameter. It can be found in the absence of arteriosclerosis. Friedenwald and Ashton have done much to clarify the nature and development of the microaneurysm. The microaneurysm may form as an outpouching at the bifurcation, or other parts, of the capillary or at loops in the

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* Lukens and Dohan [1] found lesions in the glomeruli of a dog made diabetic with beef pituitary extract which resembled early changes of intercapillary glomerulosclerosis. These authors, however, did not describe glomerular nodules.

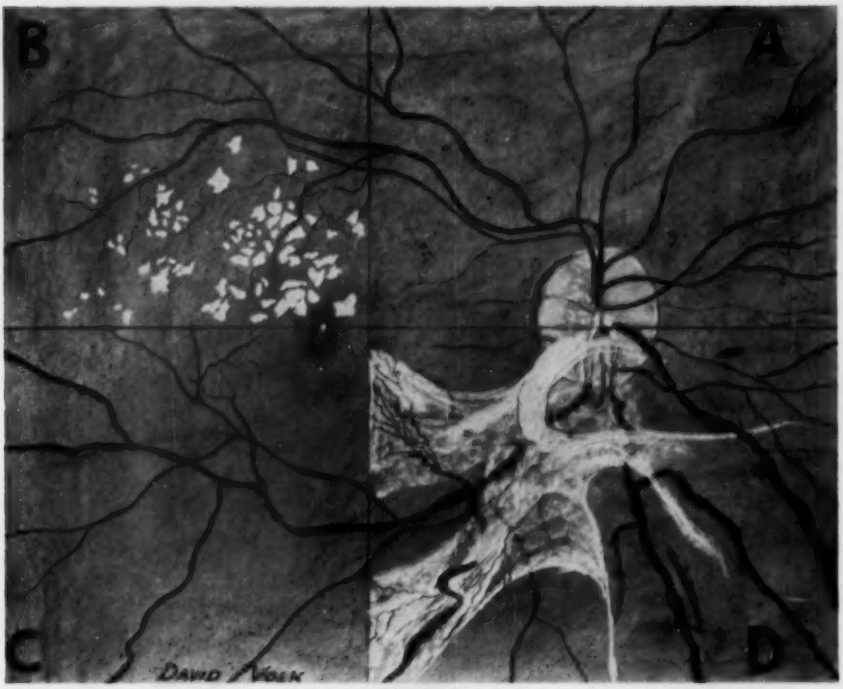

Fig. 1.—My composite drawing showing the characteristic ophthalmoscopic appearance of the individual components of diabetic retinopathy. Quadrant *A* shows numerous capillary microaneurysms and punctate hemorrhages. Quadrant *B* shows sharply demarcated irregularly shaped yellowish-white to white "hard" exudates. Quadrant *C* shows venule dilation and varicosities. Quadrant *D* shows abundant fibrous tissue and new vessel formation involving the retina and vitreous body (retinitis proliferans). Venule changes as in (*C*), but severer, are shown. There are also two superficial flame-shaped hemorrhages. Lesions as in *A* may be the only type of defects seen. Lesions as in *C* are usually associated with those of *A*, although dilation of the veins and venules may be seen alone. Lesions as in *B* are always associated with those of *A* and often with those of *C*. Lesions as in *D* are preceded and accompanied by the changes shown in *A*, *B*, and *C*. (Courtesy of Dr. Joseph I. Goodman and *American Journal of Ophthalmology*, Ophthalmic Publishing Co., 36: 957, 1953.)

capillary, the loops forming by elongation and kinking of the vessel. The inner portion of the capillary loop may become obliterated, resulting in a microaneurysm. Once formed, an aneurysm may persist for a long time. Many of the aneruysms have thickened walls, in some cases to such an extent that complete occlusion of the cavity occurs. The thickened wall of the aneurysm appears to be concentrically laminated, as does the outer thickened wall of a capillary loop.

Ashton's photomicrographs depicting the development of a microaneurysm clearly show this laminated structure (Fig. 2). Ashton describes this thickened wall as laminated exudate. The nature of this thickened wall is not understood. Staining reactions with the McManus periodic acid stain indicate that it may have a high mucopolysaccharide content, the significance of which is also not clarified.

The Renal Nodule

The specific renal nodule (Figs. 3 and 4), which may be found in glomeruli which are otherwise normal except for some capillary dilation and vascular stasis,

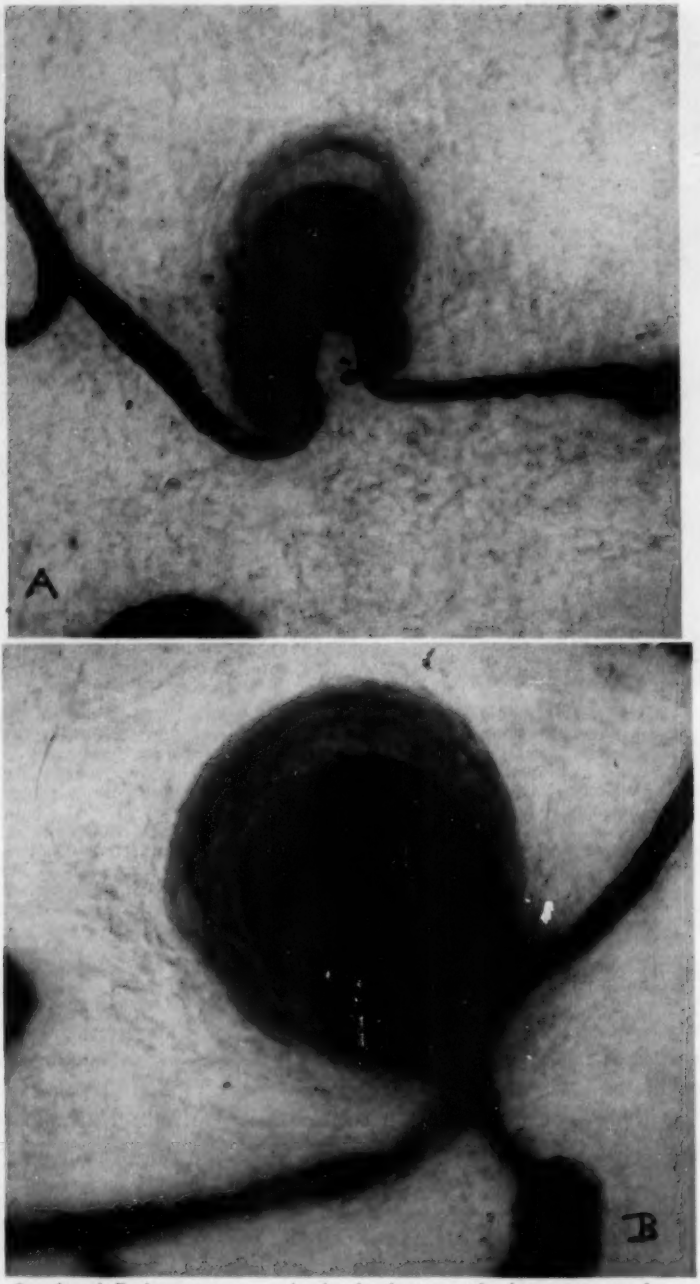

Fig. 2.—*A* and *B* show two stages in the development of microaneurysms from capillary loops. Note the concentrically laminated, finely fibrillar dense periodic acid-Schiff-positive-staining material surrounding the varicose loop and aneurysm, most prominent on the outer convex border. India ink injected; periodic acid-Schiff stain; *A*, reduced from mag. × 610; *B*, reduced from mag. × 540. (Courtesy of Dr. Norman Ashton and the *British Journal of Ophthalmology*, British Medical Association, 37 :282, 1953.)

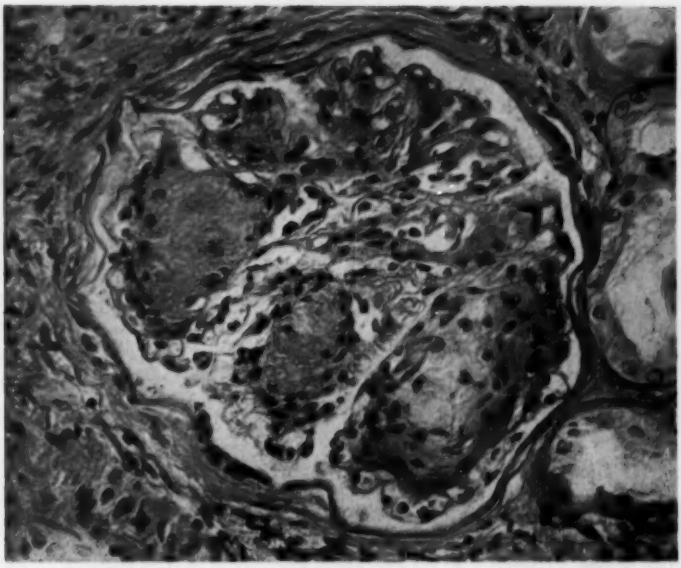

Fig. 3.—Typical appearance of a glomerulus in severe intercapillary glomerulosclerosus. Transitional stages in the development of nodules are shown. In the upper portion a very early stage in nodule formation is present. Cells and capillaries appear to be enmeshed in an irregular fibrillar substance. In the lower right is a nodule in a more advanced stage of development. It contains concentrically laminated cells and fibrils. The capillaries lie at the periphery. The remaining two nodules are well-advanced, with central hyalinization. Cells and capillaries are concentrically arranged at the periphery.

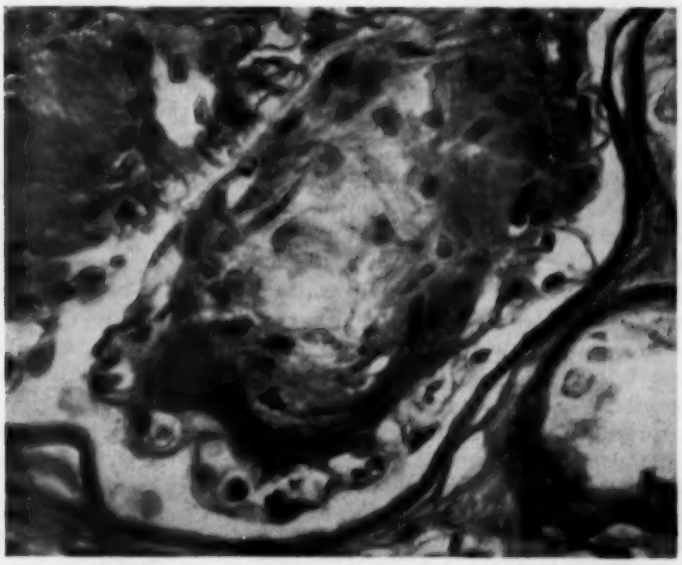

Fig. 4.—Nodule from Figure 2 ($60\mu \times 120\mu$). This photomicrograph has been specially photographed through filters so as to emphasize both the fibrillar nature and high cellularity. Many of the cells within the nodule are suggestive of fibroblasts. The high degree of cellularity and nonhomogenous staining indicate incomplete hyalinization and possibly active proliferation. Periodic acid-Schiff stain; reduced from mag. $\times$ 950.

has its own characteristic appearance. The nodule, or nodules, are generally found in the periphery of the glomerulus. They vary from 20μ to 120μ in diameter and consist of circumferentially laminated finely-fibrillated hyalin containing some cells within and one or more layers of cells at the periphery. A layer of capillaries surrounds the nodule, and one or more capillaries may be seen within the nodule.

The presence of cells within and at the periphery of the nodule suggests that the cells may be responsible for the growth of the nodule. The nodule takes a connective tissue stain, but other staining reactions indicate that it may have a high mucopolysaccharide content. There is a notable absence of inflammatory cells within the glomeruli. Arteriolosclerosis of the afferent arteriole, and very often the efferent arteriole, is almost always found in association with the glomerular nodules.

The evidence seems to indicate that the nodule is a localized mass of dense collagenous connective tissue which is hyalinized.

Differences Between the Specific and Renal Lesions

The specific retinal lesion may occur early in the clinical course of the diabetes, need not be associated with hypertension or arteriolosclerosis, and does not in itself carry a bad prognosis as to the life expectancy of the patient. The specific renal lesion generally occurs later in the course of the disease and is commonly associated with generalized arteriolosclerosis, hypertension, albuminuria, and generalized edema. The clinical picture is known as Kimmelstiel-Wilson disease, and the prognosis is poor.

There is a considerably greater prevalence of the specific retinopathy as compared with the prevalence of the specific renal lesion. Ashton [2] presented data on postmortem material, including the eyes of 110 diabetic subjects. Retinopathy in various stages was present in 68%, and Kimmelstiel-Wilson disease was seen in 36%. In this series, as the retinopathy became severer, the evidence of nephropathy became increased, so that the severest retinopathies were almost always associated with the renal lesion. Furthermore, Kimmelstiel-Wilson disease did not occur in any case in the series without retinopathy.

The dilated capillaries of the glomerulus may be analogous to the retinal microaneurysms, but evidence of actual microaneurysms in the glomerulus has not been clearly demonstrated. The hyalinized renal nodule apparently develops and increases in size as a result of progressive proliferation of connective tissue about normal-sized or dilated glomerular capillaries, whereas the hyalinized retinal microaneurysm, which resembles the renal nodule, develops first as a microaneurysm which gradually becomes obliterated by what may be connective tissue proliferation. Capillary budding occurs in the retina, but evidence has not been presented demonstrating capillary budding in the glomerulus. Hemorrhages occur frequently from the retinal capillaries but rarely from the glomerular capillaries. The retinal lesions are predominantly venous except after the development of the Kimmelstiel-Wilson phase, at which time the appearance of the retina indicates arterial involvement, while the renal lesions must be considered arterial on the basis of the function of the capillaries, filtration only, and their location between two arterioles. Furthermore, it should be pointed out that the retinopathy of Kimmelstiel-Wilson disease is no longer a simple "diabetic retinopathy" but takes on many of the characteristics of hypertensive-arterio-

sclerotic retinopathy, such as arteriolar involvement, flame-shaped hemorrhages, and fluffy exudates. Ashton [3] has reported extensive arteriolar and precapillary arteriolar wall hyalinization as a characteristic late development in the diabetic process. This is in contrast to the early stages of diabetic retinopathy, in which no hyalinization or other structural changes can be found in the arterioles and precapillary arterioles.

It seems likely that the development of the Kimmelstiel-Wilson glomerular nodule and the almost invariable concomitant glomerular arteriolosclerosis heralds the development of similar arteriolar pathology in the retina. The ensuing characteristic retinopathy could very well be termed "retinopathy of Kimmelstiel-Wilson disease," in contrast to "diabetic retinopathy," in which the pathology may be limited to the capillary microaneurysms, venule varicosities, small deep hemorrhages, and sharply demarcated exudates. The above concept serves to explain Ashton's [2] postmortem findings of a high percentage of diabetic retinopathy without Kimmelstiel-Wilson disease and also his findings of retinopathy in every case of Kimmelstiel-Wilson disease. Once intercapillary glomerulosclerosis develops, the retinopathy of Kimmelstiel-Wilson disease develops. Hence all diabetics dying with intercapillary glomerulosclerosis will show retinopathy.

Summary

The differences between the specific retinal and renal lesions with regard to time of onset, mode of development, relative prevalence, histological differences, and prognosis make it logical to assume that there are basic differences in the pathogenesis of the two lesions and that they may be unrelated except for the fact that both occur in human diabetes mellitus.

Unless sufficient valid data are presented establishing the similarity of the retinal and renal lesions in the human, caution should be used in interpreting the pathogenesis of retinal lesions from evidence related to the renal lesions.

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Pseudostrabismus Caused by Heterotopia of the Macula

Report of a Case and Review of the Literature

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and
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All of us are familiar with the relatively common pseudostrabismus caused by an exaggeration of the angle gamma or, as some prefer, angle kappa. In such cases, the alternate cover test quickly rules out the presence of an actual heterotropia, and the normal position of the blind spots in the visual fields rules out the presence of an anatomical anomaly. However, a condition does occur in which there is an actual physical derangement of the relationship of the blind spot, or optic papilla, to the macula.

Idiopathic heterotopia of the macula is a very rare and interesting condition. It is typically manifested by eccentric fixation in an eye with good visual acuity and produces a confusing pseudostrabismus. The first report of this bizarre anomaly was that of Bernhard [1] in 1898. He recorded a case wherein the left eye appeared to be looking downward, when it was actually looking straight ahead. Examination showed that the macula of the left eye was inferior and lateral to its expected position. This caused an apparent right hypertropia, which functionally did not exist. Other abnormal findings in the left eye were microcornea and peripheral pigmentation of the retina. In 1912 Adam [2] presented the second case. His patient appeared to have a divergence and sursumvergence, which on testing were found not to be present. The condition was unilateral, with one macula (he did not state which) being displaced upwards and outwards.

In 1913, Kruger [3] described a case in which both maculae were displaced outward, the right also being downward and the left upward. This caused an apparent exotropia and left hypertropia, but he states that the patient actually had an esotropia. Triebenstein [4] reviewed the literature to 1919 and presented two cases of his own in a mother and son. In addition to the three we have already mentioned, he cited cases by Lange,[5] Pfluger,[6] Derzhavin,[7] and Doesschate.[8] To go over these briefly, we were unable to accept Lange's case and Pfluger's, as this condition was merely assumed, and not demonstrated by examination. Derzhavin's case appears authentic, as described, but we were unable to acquire the original report. Doesschate's case did not meet our criteria for heterotopia maculae.

Triebenstein's cases were described thoroughly and were typical of this condition. The son had an upward and outward displacement of the right macula and downward and outward displacement of the left. In the mother, the left fovea was considered to be displaced upward and outward. Her retinae could not be examined satisfactorily because of cortical cataracts. Although the son appeared to have exotropia, his muscle balance was normal,

and the mother had an esotropia, even though her condition should cause a pseudoexotropia. In both cases peripheral pigmentation was observed. Triebenstein suggested that anomalies of the vessels were responsible for the heterotopia and this, in turn, was due either to an intrauterine inflammation or a preformed deficiency in the retinal embryoplasm.

Beselin [9] described a bilateral case wherein he ascribed the upward displacement of both maculae to traction from scar tissue in the superior periphery. This brings up the question of heterotopia due to trauma. This, of course, is a common condition, including such cases as retinal detachment, involving the macular area. These cases are of little interest to us, because visual acuity is usually so deranged by the trauma that the paradoxical fixation does not occur. Reports of heterotopia due to trauma, then, such as those of Stein, Fuchs, and von Szily * are not germane to this discussion.

Bielschowsky [13] described a bilateral case in 1930. Here, an apparent right hypertropia proved to really be a left hypertropia. The right macula was deviated upward, and the left, downward.

Friedman [14] described a case involving only the right eye, associated with a paramacular disciform retinal lesion.

Cohen and Weisberg [15] reported the 10th case in 1950. Here, again, an apparent exotropia and left hypertropia were really an esotropia and right hypertropia. The right macula was displaced downward and outward, and the left, upward and outward. In this case no peripheral pigmentation of the retina was seen. It was the privilege of one of us (H.H.) to examine this case at the time, and a lasting impression of this bizarre condition was retained.

Blaxter [16] reported a case involving the left eye only. As in the original case of Bernahard, the left cornea was smaller, and there was peripheral pigmentation of the retina. Despite the apparent left hypertropia the muscle balance was normal, as the macula was displaced upward from its normal position.

Finally, Duke-Elder [17] briefly describes the condition and refers to cases reported by Brewerton [18] and Kraupa.[19] However, we could not accept these as being true cases of heterotopia maculae.

We consider our case to be the 12th in the literature. It, too, is unilateral, and presents the salient features of the cases previously mentioned. For the sake of comparison, all the cases are listed in the accompanying Table. In addition to the heterotopia, features found in many of the other cases are peripheral pigmentation of the retina, anomalous courses of the retinal vessels, persistence of the hyaloid artery or its remnants manifested as membranes or floaters, and a peripheral colobomoid lesion. The association of true strabismus with this condition appears to be fortuitous, although the relatively high incidence would suggest that there is a fault in development which would predispose to both the strabismus and the heterotopia.

Report of Case

A 25-year-old white man was first seen by one of us (J. W. L.) on Feb. 23, 1955, with the chief complaint of discomfort in the right eye, aggravated by close work.

* References 10-12.

Comparison of Reported Cases

Case No.	Author	Year	Laterality	Position of Macula		Apparent Strabismus	Retinal Pigmentation	Other Findings
				Right	Left			
1	Bernhard	1898	Unilateral		Down and out	Right hypertropia	Yes	Microcornea, coloboma
2	Adam	1912	Unilateral		Up and out	Exotropia and left hyper	Not mentioned	Hyaloid remnants (?)
3	Kruger	1913	Bilateral	Down and out	Up and Out	Exotropia and left hyper	Yes	Esotropia
4	Derzhavin	1896	Unilateral		In	Both eyes deviated right	Yes	Hyaloid remnants
5	Triebenstein	1919	Bilateral	Up and out	Down and out	Exotropia	Yes	
6	Triebenstein	1919	Unilateral		Up and out	Exotropia	Yes	Esotropia
7	Beselin	1924	Bilateral	Up and out	Up and out	Double hypertropia	Yes	Marked retinal scarring
8	Bielschowsky	1930	Bilateral	Up	Down	Esotropia and right hyper	Yes	Exotropia and left hyper
9	Friedman	1942	Unilateral	Down and in		Left hypertropia	Not typical type	Disciform retinal lesion
10	Cohen & Weisberg	1950	Bilateral	Down and out	Up and out	Exotropia and left hyper	No	Esotropia and right hypertropia
11	Blaxter	1951	Unilateral		Up	Left hypertropia	Yes	Microcornea
12	Horwich & Linfesty	1956	Unilateral	Down and in		Left hypertropia	Yes	Right hypertropia, vitreous strands, exophoria-tropia, atypical optic canal

At about the age of 8, his family and friends noted that he had a habit of closing his right eye, especially when in the sun, or bright light. At about the age of 14 he visited an eye doctor and was given glasses. He felt that they did not improve his vision, and so he discontinued their use. During that period he felt that he did not use his right eye under ordinary conditions. However, if he concentrated, and looked far to the right, he felt that he was using that eye, and noted that objects appeared smaller to him through the right eye. Ever since, he has had only a dim awareness of seeing things with the right eye. As time went on, he noted increasing discomfort in that eye when he tried to read. This was severe enough for him to change his college course from business administration to physical education. He became quite a football player and subsequently sustained several injuries to the right side of his face, including a fractured zygoma at the age of 22, which was surgically reduced.

Later that year he consulted an ophthalmologist because of pain in the right eye, headaches, and poor vision. At that time he was found to have a right hypertropia of 21Δ at 20 ft., and 11Δ at 16 in., and also a small exotropia. Glasses and prisms did not help him, and so at the age of 23 he had a 4 mm. recession of his right superior rectus. This reduced his right hypertropia, but he still complained of pain in the right eye.

Shortly after this he entered service, where he again played football and was quite comfortable until he was reassigned and had to do a large amount of desk work. Again he developed discomfort in the right eye. Associated with this were severe emotional overtones, such as feelings that people were watching him, a sensation that the right eye was closed, severe headaches, a feeling of tension, frequent blinking of the right eye, a burning sensation at the top of the head associated with the impression that all his hair was going to fall out, and a feeling that the right eye was always trying to turn outward.

On examination he was seen to be a well-developed well-nourished white man of stated age in no acute distress. He would open and close the right eyelids unduly, and at times he would reinforce this motion with an opening and closing of the jaws. His face appeared to be asymmetrical, the right side looking smaller than the left. This can be seen in the accompanying photographs. Figure 1 shows the patient at age 12; Figure 2, at 17; Figure 3, at 22, just before the recession of the right superior rectus, and Figure 4 at 25, two years after the recession. X-rays disclosed no bony cause for the facial asymmetry, but Hertel exophthalmometry showed a reading of 113.5 in the right eye and 115 in the left. In the primary position, the left eye fixing, the right eye appeared to the lower of the two.

Despite the right eye's being lower, he was shown objectively, by the use of alternate cover and prisms, and subjectively, by the use of red glass and prisms and the Lancaster test, to have a right hypertropia of 12 to 16Δ. Under local anesthesia the right eye was moved upward with forceps until its reflex was level with that of the left eye. This caused the image of the right eye to progressively move downward from that of the left eye.

External examination revealed only a tiny superficial subepithelial opacity on the cornea, just inferonasal to its center. The lens contained some fine posterior subcapsular opacities. The vitreous, which was viscid, showed

Fig. 1.—Age 12. Note depression of right eye.

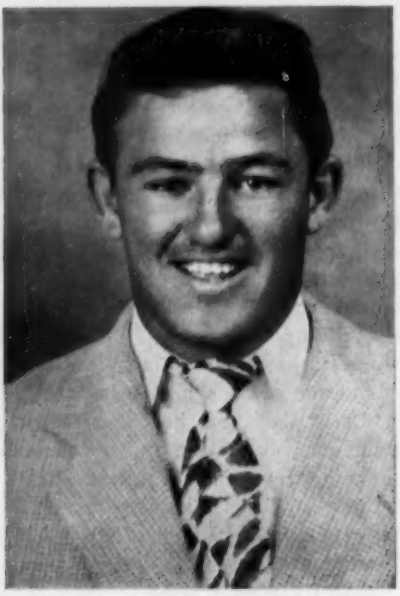


Fig. 2.—Age 17.

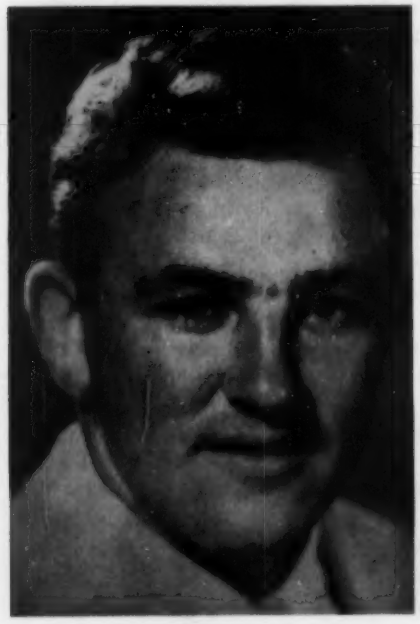


Fig. 3.—Age 22.

Fig. 4.—Age 25, after recession of the right superior rectus.

three groups of opacities, one of which was well developed and thread-like, extending posteriorly from just behind the lens.

Vision in the right eye was 20/20− correctable to 20/20 with +0.50 −1.00 10, and in the left eye it was 20/20, accepting +0.50−0.50 axis 180 for no change.

The appearance of the right fundus is diagrammed in Figure 5, and the

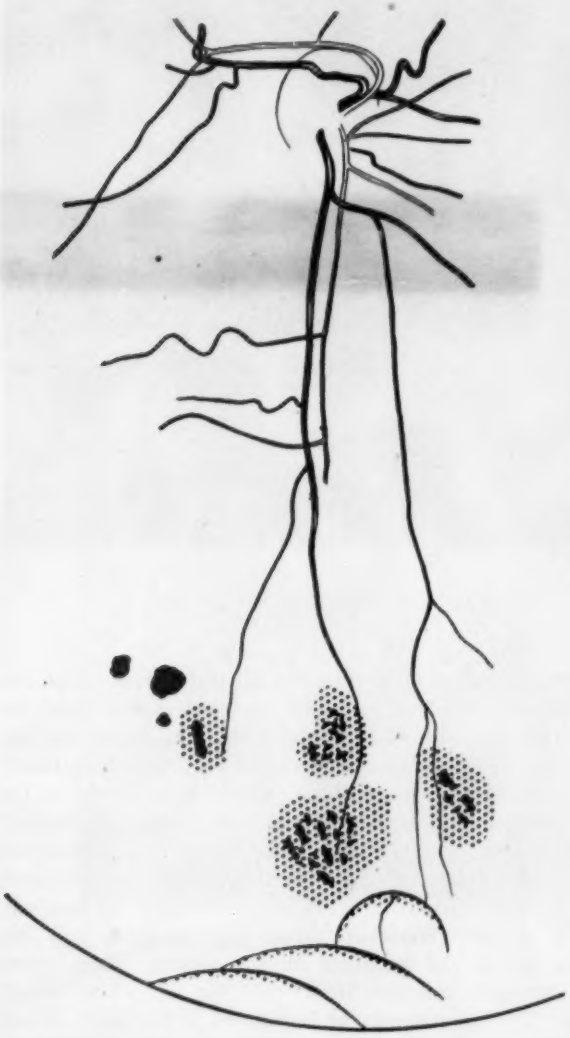


Fig. 5.—Diagram of right fundus. Macula is seen as a small dot in 7 o'clock meridian.

posterior pole is drawn in Figure 6. For comparison of the posterior poles, fundus photographs are shown in Figure 7, *A* being the right eye and *B* the left. The first striking feature is the disc. It appears to be elongated below by a sheaf of white fibers springing inferiorly and partially obscuring the vessels. When first seen this sheaf gave the impression of being raised, but

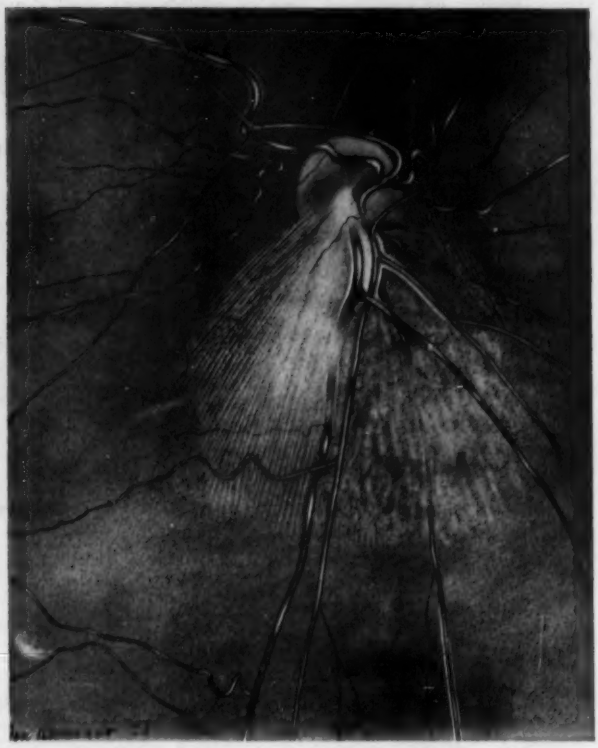


Fig. 6.—Drawing of posterior pole of right fundus (from color painting). Fovea is small white spot.

study with the binocular ophthalmoscope revealed no true elevation of this area. In addition to the sheaf effect, one gets the impression from the coloring of the disc and the position of the vessels that the right disc has rotated half a turn clockwise, so that its nasal portion may now be inferior. The major division of the veins shows sheathing. On looking lateral to the disc, no macular area is seen, but merely a normal retinal pattern. Further examination shows that the macula is inferior and medial to its normal position, being about two disc diameters from the disc in the 7 to 8 o'clock meridian. This macula appears normal in every respect except its position. On continuing outward in this meridian, some pigmentation and depigmentation is seen, as in an old localized chorioretinitis. Then, more peripherally and almost straight inferior from the disc, a white tiered, lobulated lesion is seen. To some extent it resembles a localized retinal detachment. It could barely be seen with the direct ophthalmoscope and had to be examined with the indirect. Even with the latter it was impossible to see peripheral to this lesion. Only its proximal tier bore retinal vessels. It was slightly elevated, but how much was apparent elevation due to its peripheral location and how much was actual could not be accurately determined. There were some pigmentary changes near its lateral margins.

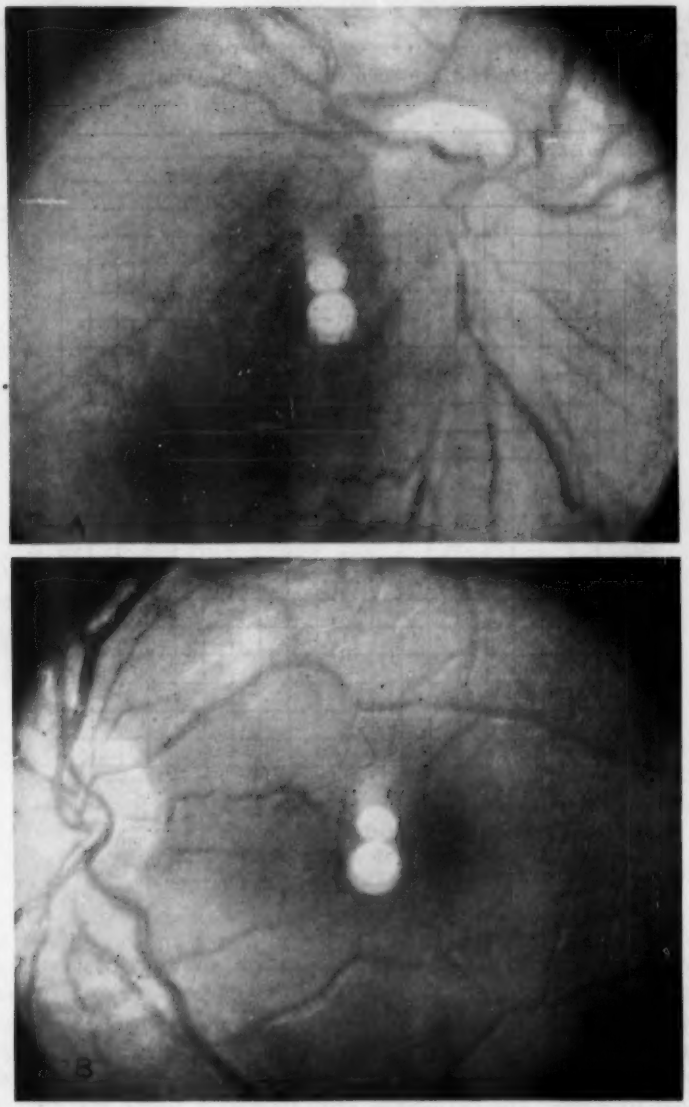


Fig. 7.—*A*, photograph of right fundus (from a Kodachrome film). *B*, photograph of left fundus (from a Kodachrome film).

With the pupil widely dilated and with use of a contact glass, the crown of the lesion could be seen with the slit lamp, but that was all. There was no pushing forward of the iris, and transillumination was negative.

Thorough examination of the left fundus showed only a tiny area of degeneration at 10 o'clock, so peripheral that it could be seen only by indirect ophthalmoscopy.

Study of the muscle balance showed a rather comitant right hypertropia and exotropia. The former ranged from about 14 to 20Δ, and the latter,

from 0 to 8Δ. Greatest deviation was on gaze down and to the right, suggesting right inferior rectus paresis or left superior oblique overaction. The results of the Lancaster test are seen in Figure 8. These checked well with

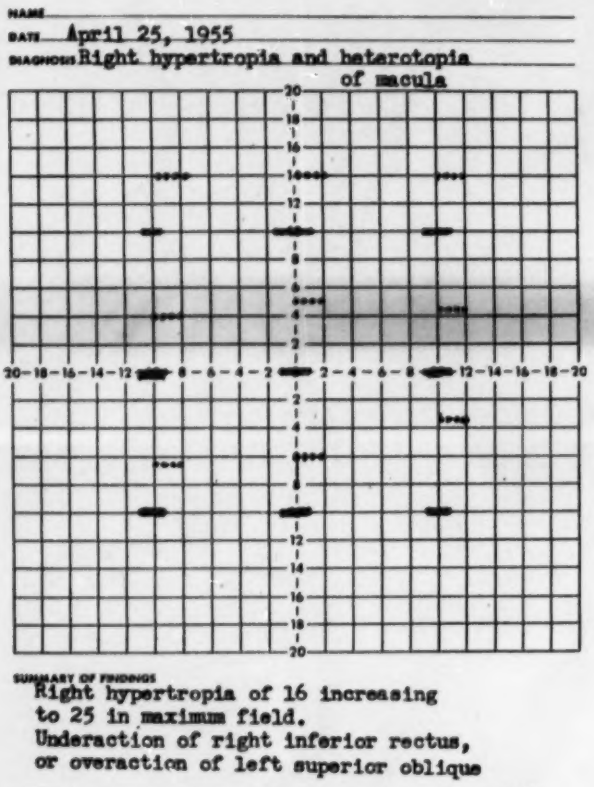

NAME
DATE April 25, 1955
DIAGNOSIS Right hypertropia and heterotopia of macula
SUMMARY OF FINDINGS
Right hypertropia of 16 increasing to 25 in maximum field.
Underaction of right inferior rectus, or overaction of left superior oblique

Fig. 8.—Result of Lancaster red-green test, left eye fixing.

the cover test. The amblyoscope examination showed a normal retinal correspondence, first degree fusion, momentary second degree fusion, and intermittent suppression.

Visual field studies, as seen in Figure 9, showed the blind spot of the right eye to be elongated and shifted downward, as would be expected from the fundal findings. The peripheral field showed a slight notching above, corresponding with the peripheral lesion in the inferior zone of the retina. X-rays showed perfect healing of the old fracture of the zygoma. There was no asymmetry of the facial bones, but the right optic foramen, as seen in Figure 10*A*, was seen to be horizontally oval, as compared with the more normal-appearing, vertically oval, left optic foramen seen in Figure 10*B*.

The only other abnormality found in the examination of this patient was tinnitus. This was really a "rushing" sensation in his head, synchronous with his systole. No bruit could be heard with the stethoscope. Audiograms showed depression in the higher frequencies.

It was felt that there were two possible ways of treating this man's

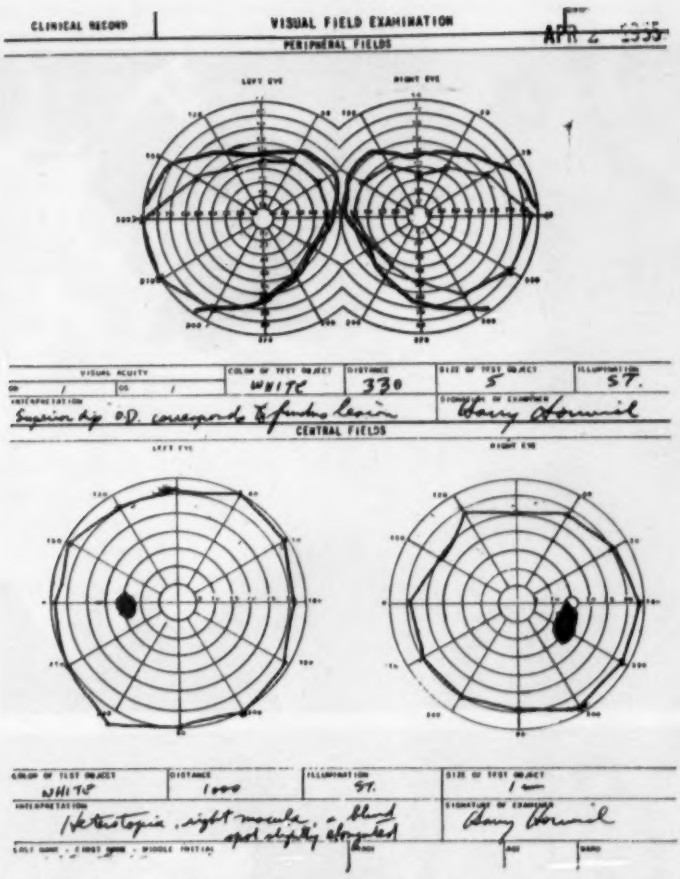
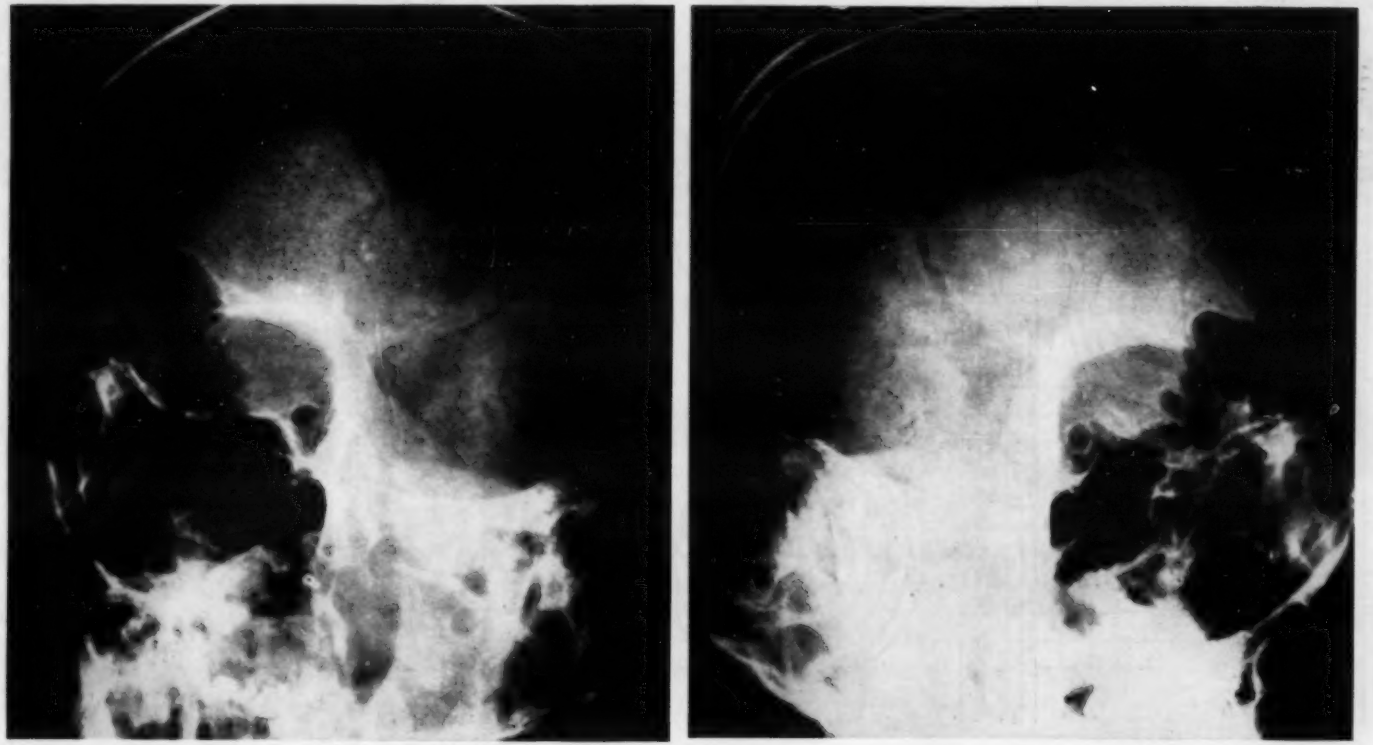


Fig. 9.—Visual fields. Note enlargement and displacement of right blind spot in central field and superior notching in right peripheral field.

ocular condition. One would be to raise the right eye and thereby separate the images even more and possibly improve his appearance and comfort. The other would be to lower the right eye even more, giving him a chance to fuse more easily but making his appearance worse. For extraneous reasons, neither procedure was done, and he was discharged from clinic.

Comment

The Table shows that the displacement of the ectopic macula may be in almost any direction. The interesting thing about this is that almost every case was associated with some peripheral lesion resembling chorioretinitis. In some cases the muscle balance was perfectly normal despite the apparent deviation (Blaxter); while in others, such as ours, there was a genuine muscle imbalance as well. Whether or not these cases were congenital could not be definitively established. In many of them there were other anomalies (such as coloboma, microcornea, bone changes, etc.) which strongly suggest a congenital basis. In one case, though (Stein),



A

Fig. 10.—*A*, x-ray of right orbit. Note horizontally oval optic canal.

B

B, x-ray of left orbit. Note more normal vertically oval optic canal.

the condition was definitely seen to follow trauma, and in another (Friedman) it was believed to have followed a birth injury. An interesting point is that, in all pictures of this condition which we have been able to find, the macular vessels in the area to which the macula is displaced show little derangement, but the macular vessels in the area from which the macula has been displaced give a marked appearance of traction, sometimes showing a hairpin turn from their normal direction.

Dr. Aeleta Barber was kind enough to consider this case for us from the embryologist's point of view. In her opinion, the changes causing this apparent rotation of the retina could have been developmental (primary) or mechanical (secondary).

Considering a primary causation, she stated that congenital displacement of the macula may result from abnormal changes in the relative rate of growth in different parts of the retina. In the early stages of development the growth rate in the macular region is precocious; then by the third month the rate decreases and differentiation in the macular area lags behind that in the surrounding retina until the seventh month, when the rate of development becomes markedly accelerated again. During this time there has been an increase in the area of the retina and in the size of the eye, so that abnormal variations in the growth rate of either the retina proper or of the macula would result in shifting the position of the macula from its usual location.

As for a secondary causation, mechanical displacement of the macula may result from traction such as adhesion of blood vessels in the primary vitreous to the inner surface of the retina, or by the proliferation of retinal strands such as would follow fetal retinitis. The presence in this case of opaque strands in the vitreous, and what is probably a retinal detachment inferiorly, would certainly fall in well with this. Other authors also have noted traction bands in these cases, and this would suggest a common causation. The area inferiorly, where these changes exist, approximates the original site of the fetal fissure, but whether or not defective closure of the fissure is responsible for the heterotopia of the macula is impossible to say.

It is probable that this condition is not as rare as the meager literature would suggest. Since it is rarely looked for, it would be recognized only in its more gross forms. The havoc it wreaks with one's expected findings in a muscle-balance study makes the condition entertaining, to say the least.

Summary

The literature on heterotopia is reviewed, 11 bona fide cases being found, 2 of which are from the United States and 1 from Britain.

A case, probably congenital, is presented.

Theories concerning the origin of this condition are advanced.

Aeleta B. Barber, Ph.D., of Louisiana State University, considered the embryologic factors in this case, and Prof. James H. Allen and Mr. Don Alvarado, of Tulane University, prepared the illustrations.

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A Survey of the Pathogenesis of Retinal Venous Occlusion

Emphasis upon Choice of Therapy and an Analysis of the Therapeutic Results in Fifty-Three Patients

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and
JOHN H. OLWIN, M.D., Chicago

A review of the clinical and histopathologic features of occlusion of the central retinal vein and its main tributaries is indicated at the present time for two reasons:

1. We have accumulated during the past decade considerable experience in the use, including prophylactic application, of a variety of anticoagulants.

2. In the near future, a new method of prothrombin level determination * is going to be generally available, which appears to combine the accuracy of the two-stage method with the ease and rapidity of the one-stage method now in general use. Thus, further elimination of the hazards of anticoagulant therapy may stimulate new interest in its use for retinal venous occlusions.

The first part of the following study deals with the histologic analysis of 21 eyes in which there was an occlusion or an imminent occlusion of the central retinal vein and with the demonstration, in each case, of the occlusion mechanism.

Only material in which detailed clinical histories and medical findings were available was chosen for this study. A number of these eyes were observed clinically for a varying length of time by one of us (B. K.).

Part I

The pathogenesis of occlusion of the central retinal vein or of one of its main branches is always complex. Several factors are responsible for it, but one of them usually so dominates the clinical course of the occlusion and the histopathologic picture that a classification into three types of occlusive mechanisms is possible by correlating the clinical and histological features.

In this material, of 21 selected eyes, either serial cross sections of the central vessels throughout their intralaminar course and, as far as material was available, through their retrolaminar course were made or the longitudinal course of the vessels was reconstructed from serial meridional sections.

A. Occlusion by External Compression

In nine eyes of this series, the dominant factor in the pathogenesis of the occlusion was external compression with secondary endothelial proliferation

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* Arscott, P. M.; Koppel, L. J., and Olwin, J. H.: Unpublished data.

(Table 2). This group also includes two of the eyes with impending occlusion.

In the course of an essentially chronic sclerotic atrophic process which affects the central artery, the central connective tissue strand, and the cribriform plate, the aperture of the vein is gradually narrowed by external compression. Whenever the venous compression has reached a stage of closure of the lumen at one or more places, secondary irritative proliferation of the endothelium accelerates the obliteration of the lumen. The stage of slit-like narrowing of the lumen predisposes to secondary thrombus formation. This event may be precipitated by any condition causing stagnation in the retinal circulation. The coexistence of unfavorable anatomic relations between the vessels, or other anomalies, such as a large glial meniscus at the floor of the physiologic excavation, may accelerate such thrombus formation.

It will be noted that the onset of the occlusion was sudden in four of the patients in this group and rapid (within a few days) in one, while only two patients had prodromal symptoms, for 6 and 24 months, respectively.

Two of the sudden occlusions and the rapid one developed in patients with essential hypertension, one of them also a diabetic; another, in a patient with diabetes only, both conditions which may produce hemodynamic disturbances in the retinal circulation.

In two of the sudden occlusions occurring in patients with a systemic disease there was also some evidence of primary venous disease in the form of endothelial cushions and detachments of the endothelial lining in locations other than the site of occlusion. The three other cases, with sudden and rapid onsets, presented histologically pure pictures of the sclerotic compression type. The element of stagnation was suggested by the clinical findings.

Of the two patients in this group with slowly developing occlusions, one, 54 years of age, had an essential hypertension of short duration and normal retinal vessels in the other eye; the other, 72 years of age, had normal blood pressure and only incipient retinal angiosclerosis in the fellow eye. Both presented the typical histopathologic picture of occlusion by external compression. In one of them there was an indication in two places of a collateral pathway to the ciliary vascular system in the choroid.

Patients with this type of occlusive mechanism, an essentially slow process, are the most promising ones for prophylactic anticoagulant therapy. The aim of the therapy here is postponement of the inevitable occlusion to a time when collaterals are sufficiently developed to replace the original venous pathway.

Therapy in a fully established occlusion of this type is of little or no value unless it is precipitated by an episode of stagnation with thrombus formation at a time when the venous aperture is not yet too narrow. A reopening of the narrow lumen may be accomplished occasionally by very prompt initiation of anticoagulant therapy. Some of the patients discussed in Part II suggest such an event.

B. Occlusion by Stagnation and Primary Thrombus Formation

The prerequisite for a stagnation thrombosis is a relatively sudden slowing of the venous circulation in the retina, which may reduce the pressure within the central vein or its main tributaries to a point so much lower than the intraocular pressure that the vein collapses at the point where its pressure is lowest.

The causes of the reduced speed in the venous circulation are manifold, viz., arterial spasms, sudden reductions of blood pressure, blood dyscrasias, and many

other conditions, which are mentioned in Part II of this paper.

The histopathologic diagnosis of stagnation thrombosis is made by exclusion of the two other mechanisms and by detailed knowledge of the history and clinical findings.

Two of our patients representative of this type, 41 and 56 years of age, respectively, had malignant hypertension and marked spastic contraction of the retinal arterioles of the other eye.

Cross sections of the optic nerve and central vessels of the younger patient, with malignant hypertension of short duration, revealed absence of sclerotic changes in cribriform plate and central connective tissue strand. Pathologic findings in the central artery were limited to irregular endothelial proliferation and hypertrophy of the elastica interna. Muscularis and adventitia were of normal appearance. The central vein was not compressed, merely collapsed, forming a triangular aperture, which was further narrowed by subendothelial proliferation around the pointed collapsed angles. There was no thickening of the venous walls. Signs of primary venous disease were absent.

Meridional sections of this eye revealed marked hyalinization of the retinal arterioles.

In the older patient with malignant hypertension, cross sections through optic nerve and central vessels revealed a normal central connective tissue strand and an uncompressed vein. The walls of the central artery, whose lumen was collapsed, were only slightly thickened by hyperplasia of the internal elastic lamella. The oval lumen of the vein was occluded by a fibrous plug throughout its intralaminar course.

Meridional sections of this eye also showed marked hyalinization of the retinal arterioles.

In both cases (Cases 32-21 and 33-48) there was a striking discrepancy between the amount of sclerosis of the central artery and that of the retinal arterioles. The central arteries did not show the rigid circular cross sections which were seen in the eyes of patients with advanced essential hypertension or arteriosclerotic disease and thus did not encroach upon the central vein.

The fibrous plug in the central vein of the older patient could be interpreted as an organization product of a thrombus (the eye was removed six months after the occlusion) or as a mixture of endothelial proliferation and organization of a thrombus. There was, however, no evidence of widespread primary venous disease.

In the third patient of this group a reconstruction diagram of the central vessels revealed complete collapse of two of three main tributaries and an extreme narrowing of the central vein by endothelial plaques and by a partial detachment of the endothelial lining resembling a dissecting aneurism. These findings point to a factor of primary degenerative venous disease in the pathogenesis of this occlusion. There was also an element of compression in it, represented by an unusually large glial meniscus. The complete collapse of large tributaries to the central vein and the overnight loss of vision in this aged patient suggest stagnation as the predominant factor in this venous occlusion.

C. Occlusion from Primary Venous Disease

Five patients of Group C revealed the degenerative type of primary venous disease as the predominant element in the pathogenesis of the occlusion, and four, the inflammatory type. One of the former was still in the imminent stage.

The inflammatory condition was still in an active stage in three of the eyes, and in the other there were lesions suspected to be end-stages of an inflammatory process.

1. *Degenerative Venous Disease.*—The findings interpreted as primary venous disease of the degenerative kind consisted of diffuse and severe lesions of the venous endothelium, such as detachments, intramural thrombus formation behind the detached epithelium, hydrops, and cushion-like proliferations of the endothelium in places other than the site of occlusion, all lesions confined to the central vein, while the central artery and the central connective tissue strand were normal or only slightly sclerosed (Fig. 1).

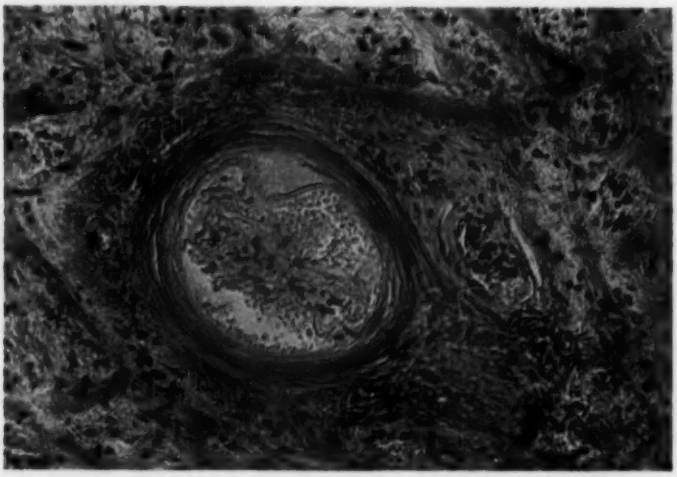

Fig. 1 (Case 52-8).—Cross section through the central vessels within the posterior half of the cribriform plate. Central artery and central connective tissue strand have normal dimensions. The central vein is not compressed but is occluded by subendothelial and endothelial proliferation; slit-like lumen.

All these patients had a severe systemic disease; three had an essential hypertension of long duration, and two, a diabetic condition, which was associated with a Grade 3 diabetic retinopathy in one of them.

Two of the severely hypertensive patients had imminent cardiac failure and cardiac decompensation, respectively. Both of these conditions are known causes for hemodynamic disturbances in the retinal circulation, which may have played some role in the pathogenesis of these two occlusions.

Two of the hypertensive patients suffered a rapid and sudden onset of the occlusion, respectively, suggesting an element of stagnation in the occlusive mechanism.

2. *Inflammatory Venous Disease.*—Two of the eyes of this group will be described in detail, because they have not been included in any previous studies of this subject and because they may represent the first attempt ever made in defining some criteria for the differential diagnosis between the inflammatory and the other types of venous occlusion.

Case 1 (55-6).—A man 29 years of age complained of blurring of his right vision first noted two weeks prior to the first visit to his ophthalmologist.

At the time of the first visit the right eye vision was 0.5; the left vision and the left fundus were normal.

In the right fundus there was edema of the disc and of the adjacent retina and multiple hemorrhages of venous type were scattered along the tremendously engorged retinal venous tree. Also a diffuse yellowish white discoloration was noted, especially in the fundus periphery.

The patient was placed on anticoagulant therapy (bishydroxycoumarin [Dicumarol]) immediately for a period of 10 days. During this period the retina became suffused with hemorrhage, and vision was reduced to light perception.

A complete medical examination, including bone marrow studies and blood cultures, was negative, excepting a 2+ reaction to tuberculin (first strength).

Within four months the right eye became painful, with a secondary glaucoma (Schiøtz 68.0). There were still massive retinal hemorrhages and an extensive whitish discoloration of the fundus periphery. The vitreous was clear throughout the period of observation.

The eye was removed because of intractable pain five months after the occlusion of the right central vein had become complete.

Histopathologic Findings.—The bulb was fixed in formalin and sectioned horizontal plane after cross sections through the optic nerve had been made beyond serially in the anterior surface of the cribriform plate.

Meridional Sections.—The anterior segment revealed extensive peripheral anterior synechiae and the characteristic very vascular fibrous membrane over the anterior surface of the free portion of the iris, which had caused an eversion of the pupillary border. The atrophic iris and the ciliary body contained a mild diffuse infiltration with plasma- and plasmacytoid cells. The choroid, although shrunken by fixation, appeared normal.

There was tremendous gliosis of the retina, which also contained pigment-laden phagocytes and small cavities filled with hemorrhagic debris. Throughout the outer half of the posterior polar region of the retina there was dense infiltration with fatty granular cells. The percipient retinal elements were completely destroyed, and their place, between external limiting membrane and pigment epithelium, was taken by a thick almost continuous layer of fatty granular cells (Fig. 1). These undoubtedly were responsible for the diffuse yellowish white discoloration repeatedly mentioned in the clinical description of the fundus.

The vitreous was detached from the retina only in a few circumscribed places, and the subvitreal space was filled with transudate containing a few erythrocytes and fatty granular cells.

The optic papilla also revealed diffuse glial proliferation; no intact nerve fiber bundles were found. Some retinal arteries were of normal caliber; some had distinct vasa vasorum; in others the lumen was slightly narrowed by subendothelial proliferation. Many small venous branches in the nerve head and the adjoining retina were obliterated by endothelial plugs; others had dilated apertures and some lymphocytic cuffing.

Cross Sections Through Nerve and Central Vessels.—Throughout the retrolaminar course the lumen of the central artery was evenly round, with normal walls, and well filled with blood. Within the posterior half of the cribriform plate the arterial walls were slightly wrinkled but the aperture was still good and well filled with blood. Throughout its anterior intralaminar course the central

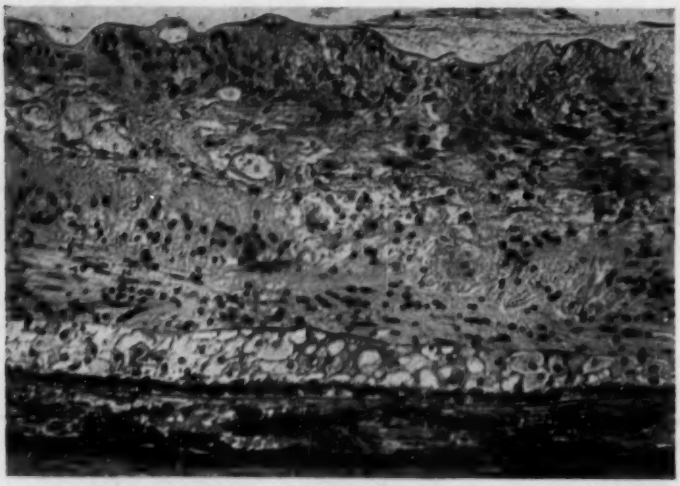

Fig. 2 (Case 55-6).—Meridional section through retina and choroid. Marked gliosis of retina, dense layer of fatty granular cells in subretinal space, similar phagocytes also creeping through retina.

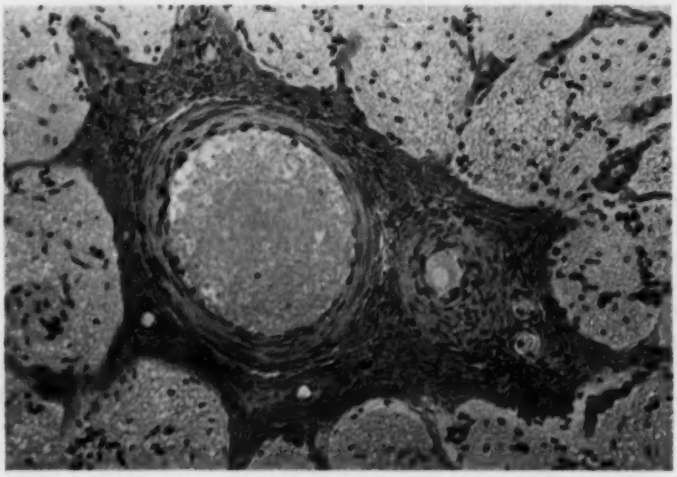

Fig. 3 (Case 55-6).—Cross section through central vessels in retrolaminar region. Central artery and central connective tissue strand normal; lumen of central vein narrowed by thick walls, containing slight lymphocytic infiltration.

artery was completely collapsed and empty, but it had an entirely normal appearance otherwise (Fig. 5).

The main pathologic findings in the central vein were in its retrolaminar portion. The first 50 cross sections revealed its lumen to be rather narrow, with thick fibrotic walls and slight lymphocytic infiltration (Fig. 3). Within the following 100 sections the lumen became progressively narrower, the thickened wall densely infiltrated with lymphocytes (Fig. 4), until complete occlusion occurred at one place, still in the retrolaminar region. From this point forward

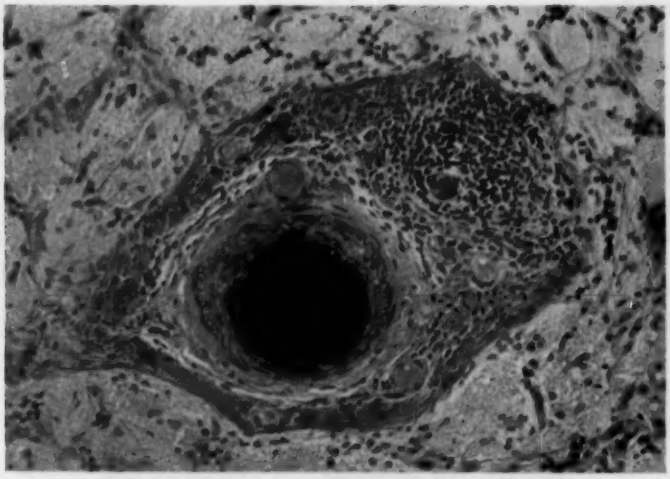

Fig. 4 (Case 55-6).—Cross section through central vessels, nearer posterior surface of cribriform plate but still retrolaminar, a few sections removed from actual occlusion. Verhoeff's elastica stain. Slight tangential section of normal central artery. Dense lymphocytic infiltration of venous wall; extremely narrow but round venous lumen.

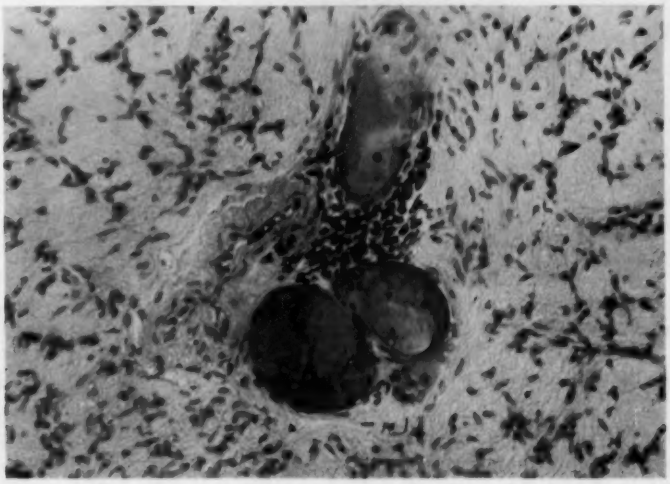

Fig. 5 (Case 55-6).—Cross section through central vessels in anterior half of cribriform plate, in front of junction of three main tributaries. Central artery completely collapsed; venous branches congested; nest of eosinophiles between venous branches.

the venous lumen became again gradually wider, containing blood and serum, with just a homogeneous mass (serum?) in the most anterior portions.

Sections through the main venous tributaries in the prelaminar area showed them filled with a similar homogeneous mass and rather dilated lumens (Fig. 5). Between these branches and the collapsed artery there was a dense focus of eosinophile leucocytes.

The retrolaminar portion of optic nerve and its sheaths was normal. The anterior portion of the nerve revealed considerable irregular retrodisplacement of the lamina cribrosa and partial atrophy with secondary glial proliferation.

Special features in this case are the following:

1. The site of the occlusion in the retrolaminar portion, not intralaminar as is the rule in the other types of occlusions.

2. The complete collapse of the artery, possibly from reflex vasoconstriction arising from intimal irritations of the vein in the course of the chronic inflammatory disease.

3. The profuse production of fatty granular cells, which caused a whitish discoloration of the fundus.

Case 2 (55-1).—A woman, 51 years of age, noted gradual blurring of the left vision several weeks before consulting her ophthalmologist. A diagnosis of papillitis was made, and intravenous typhoid injections were given. Within the following two months an increasing number of hemorrhages appeared in the retina and a tentative diagnosis of incipient venous occlusion led to use of anti-

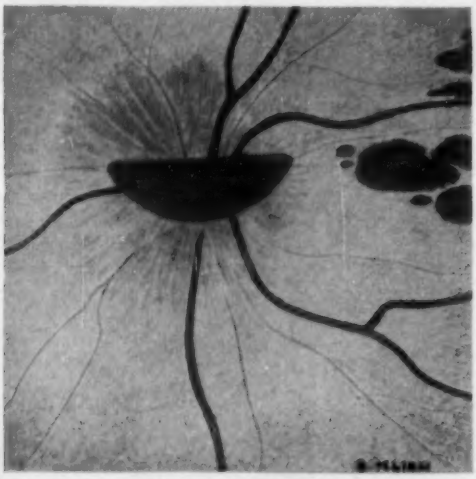

Fig. 6 (Case 55-1).—Clinical picture of four months before enucleation. Note diffuse yellowish-white discoloration of fundus, subhyaloid hemorrhage, narrow arteries.

coagulant therapy, which was terminated after three weeks because of severe hematuria.

During the following six months sudden severe pain developed radiating from the orbit to the occipital region, associated with nausea, slight left-sided facial flush, and periorbital edema.

An arteriogram and skull films to rule out an aneurism of the internal carotid artery were negative.

The ocular findings at that time were as follows: R. E. vision, normal. L. E. vision, 3/200. Schiøtz: R. E. and L. E., 17.0 mm. Hg. The right fundus revealed an incipient degree of retinal angiosclerosis; the right eye was otherwise normal.

The left bulb was pale; its anterior segment was normal; the vitreous, clear. The left fundus exhibited a striking picture (Fig. 6). Most of the optic disc was covered by a subhyaloid hemorrhage. The visible portion of the disc appeared edematous, and its gray color was interrupted by radial white streaks of fibrous tissue, indicating a long duration of the edema.

The disc was surrounded by a striking homogeneous yellowish-white discolora-

tion, which extended for 4 or 5 D.D. peripherally and which was located in the outer layers of the retina or between retina and choroid.

There was extreme narrowing of the retinal arteries and considerable dilation of the veins. A few disc-sized hemorrhages were scattered over the posterior polar region.

It was suggested at that time that the discoloration might be due to a mixture of exudate and inert lipoid masses from previous hemorrhages or be the result of a degenerative process associated with sclerosis of the vessels of the circle of Zinn.

The possibility of an inflammatory lesion was also considered. Complete tests for granulomatous diseases were negative. The patient had suffered from rheumatoid arthritis for the past 10 years, but the condition was well controlled with cortisone. A left chronic ethmoid and maxillary sinusitis had been treated

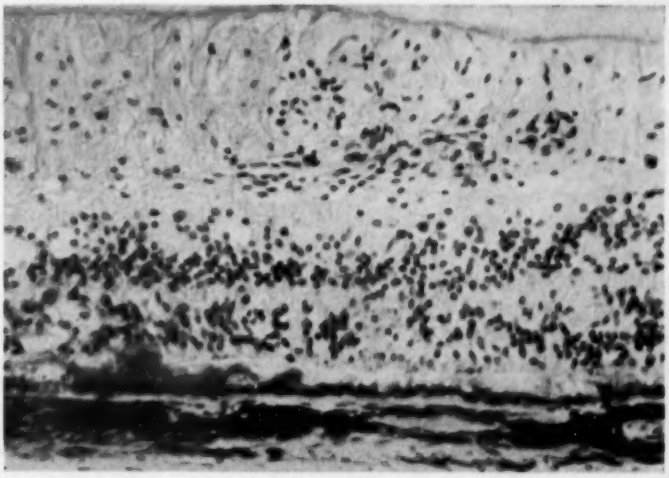

Fig. 7 (Case 55-1).—Meridional section of retina and choroid. Marked gliosis of retina; infiltration of outer half of retina with fatty granular cells; subretinal transudate with fatty granular cells, which produced white discoloration of fundus.

intermittently for the previous three or four years but had been symptomless during recent months. Blood pressure was 150/70.

For two months after this period of hospitalization the patient felt comfortable, but at the end of this period she suddenly lost the left vision completely. Several days after this event the left eye became inflamed and painful. An uncontrollable secondary glaucoma necessitated enucleation.

Histologic Findings.—The histopathologic findings in the meridional sections of this eye closely resemble those described in the preceding case (Case 55-6). The retinal gliosis was marked, but not quite as pronounced as in Case 55-6, and there was diffuse formation of fatty granular cells, which partly infiltrated the retina and partly accumulated in the subretinal space. There also was a thin layer of transudate in many places between retina and choroid (Fig. 5), replacing the neuroepithelium. There was more hemorrhage in the retina of this eye, in keeping with the shorter interval between onset of the complete occlusion and glaucoma, which were followed by enucleation within a few weeks.

There was no vitreous hemorrhage. The arteries in nerve head and retina

revealed considerable thickening of the adventitia. The central artery, which was cut meridionally through its intralaminar course, showed slight thickening of its perivascular sheath and patchy subendothelial atheromatous lesions, which narrowed its lumen.

The central vein appeared uncompressed but had markedly fibrosed and thickened walls. Its lumen carried blood beyond the posterior surface of the cribriform plate but became progressively narrower and finally disappeared in this region. At the site of occlusion, proliferation of subendothelial connective tissue and some lymphocytic infiltration was added to the fibrosis of the perivascular sheath. The central connective tissue strand had normal dimensions.

Cross sections through the retrolaminar portion of the optic nerve and central vessels demonstrated the atheromatous lesions in the central artery and the thick walls and still narrow lumen of the vein. One sector of the optic nerve in this area revealed a mild perivasculitis of the septal vessels. Some of the lymphocytic infiltration extended into the central connective tissue strand, surrounding both of the central vessels.

The inflammatory nature of this occlusion is not as obvious as that in Case 55-6 but is strongly suggested by the thickened venous walls, the absence of endothelial disease, and the inflammatory involvement of the optic nerve. The disease process was of much longer duration in this patient; consequently, more scarring and fibrosis were to be expected.

In the remaining two patients with inflammatory venous occlusion—one with syphilitic disease and chronic inflammation of the paranasal sinuses on the side of the venous occlusion, the other with tuberculosis—the fundi were not visible after the occlusion because of vitreous hemorrhages.

In the syphilitic patient, there was marked fibrotic thickening of the walls of the retinal veins and narrowing of their lumens. The eye of the tuberculous patient revealed nodules of specific granulomatous tissue projecting into the apertures of some of the retinal veins.

Comment

Primary inflammatory occlusive venous disease may have the histopathologic picture of a specific granulomatous process or may consist of nonspecific infiltration in the cases of idiopathic origin.

In the latter group, the histopathologic findings in the retina may be of a special type, characterized by tremendous gliosis, subretinal transudate mixed with fatty granular cells, and invasion of the retina with these phagocytes, findings which suggest a very slow seepage of hemorrhage over a long period of time.

The main characteristic of the resulting fundus picture may be an extensive yellowish-white discoloration, such as was visible in the two cases discussed above and in one patient of the the clinical series (Case 5 in Part II), who also gave a history of chronic sinus disease on the side where the occlusion occurred.

In all patients with the inflammatory occlusive mechanism the onset of the occlusion was very slow, a characteristic which would assure ample time for therapy if an early differential diagnosis could be made.

In all patients of Group C, the primary venous disease, whether degenerative or inflammatory, was much more extensive than the changes encountered in either the external compression or the stagnation type.

One intramural thrombus, associated with degenerative primary venous lesions, could be followed from the retrolaminar region through the entire intralaminar

course of the vein and could still be traced in the wall of one of the main tributaries in the prelaminar area (Case 50-47).

This may explain the apparently poorer prognosis with or without anticoagulant therapy of the occlusions caused by primary venous disease.

Only if we find means to differentiate clinically the inflammatory from the degenerative primary venous lesions, perhaps along the line of suggestions made in the foregoing paragraphs, can an attempt be made of intensive specific therapy for an existing granulomatous disease or of nonspecific therapy with antibiotics, perhaps combined with steroid hormones, in infectious conditions of other types.

Anticoagulants may be of doubtful value in the inflammatory occlusive mechanism, since secondary thrombus formation along a maximally diseased venous wall serves to diminish rather than to increase the hemorrhagic extravasations.

Antispasmodics, on the other hand, may prove to be useful in both types of primary venous disease in counteracting reflex vasoconstriction arising from intimal irritation. In both, also clinically observed cases of inflammatory occlusion discussed in detail above, the retinal arteries in the eye with the venous occlusion were extremely attenuated.

The element of stagnation may be more prevalent in the various mechanisms of venous occlusion than has been heretofore thought, suggesting a wider therapeutic scope for antispasmodics, especially in the prophylactic therapy of venous occlusion.

Part II

The second part of this paper consists of an analysis of the therapeutic results in 68 venous occlusions or impending occlusions (61 eyes in 53 patients).

With the exception of three patients, the choice of the anticoagulant and the prothrombin level control tests were carried out in the laboratory of one of us (J. O.).

Among these 53 patients there were 26 complete occlusions of the central vein, 8 incomplete occlusions, 14 main branch occlusions, 6 smaller branch occlusions, and 14 impending occlusions. Eleven of the imminent occlusions threatened the central vein, and three, the superior main branch.

Eight patients had bilateral involvement, and four had repeated attacks in the same eye.

For more rapid identification of the degree of venous occlusion and of the therapeutic results shown in the accompanying Tabulations, the following signs have been used.

Complete occlusion of the central vein	—
Incomplete occlusion of the central vein	=
Main branch occlusion	Y
Smaller branch occlusion	X
Imminent occlusion	=

The distinction between incomplete occlusion of the central vein and a superior or inferior main branch occlusion was made by the fundus findings alone, since the vision, although frequently much better in both types than in the complete occlusions, may incidentally be very poor because of macular hemorrhages.

The main branch occlusions, despite a similar pathogenesis, have a slightly better prognosis than the incomplete occlusions of the central vein, perhaps because the branches lie in greater proximity to the ciliary vascular system in the choroid and are capable of establishing a collateral pathway through preformed

or newly formed channels more rapidly. Since the junction of the two veins lies usually in the most anterior portion of the cribriform plate, the confining property of this structure upon the main branches is also very limited.

The division of the end-results into the four groups of good, fair, poor, and nil, as shown in the following Tabulation, is, of necessity, somewhat arbitrary.

Results	Visual Acuity	Secondary Glaucoma
Good	0.6 to 1.2	None, or temporary glaucoma (controlled)
Fair	0.1 to 0.6	None, or controlled glaucoma
Poor	Less than 0.1 but good peripheral field	None, or controlled glaucoma
Nil	No visual improvement	None, or controlled, or uncontrolled glaucoma

1. Complete Occlusions of the Central Vein

The visual end-results in this category were good in five, fair in seven, and poor in nine instances. There was one complete failure.

Various facts worth emphasizing are apparent from the accompanying Tables. In the good results the interval between initiation of therapy and onset of the occlusion was relatively short, from 24 hours to 2 weeks in all but one patient. The interval in this patient was six months, but several factors were in favor of a good result, viz., good general health, only a mild degree of retinal angiosclerosis in the fellow eye, and a sudden onset of the occlusion, suggesting some hemodynamic disturbances as part of its pathogenesis. A fourth, but in this case invisible, favorable factor must have been present in the form of preexistent effective collaterals, as indicated by the slow improvement of vision from 0.1 to 1.0 over a period of two years.

A second patient in this group of good results had a similar slow visual recovery from 0.1 to 1.0 over a span of three years, with well-visible anastomatic channels at the end of this period.

Three patients with occlusion in this group had a sudden onset, and in two it was slow.

In the group of fair results the intervals between initiation of therapy and onset of the occlusion were longer, varying from six weeks to two years. It is noteworthy that the patient with the interval of two years, a diabetic, had visible spontaneous collateral formation at the time anticoagulant therapy was initiated for an imminent occlusion of the central vein of recent onset in the other eye. In spite of the short interval the end-result in the second eye was a complete failure (the only one in our series of impending occlusions), while in the eye with the old occlusion the vision improved from 10/200 to 0.1 under the belated treatment. This eye, in which the occlusion had developed suddenly after a severe fall, obviously had preformed collateral channels which opened still further under therapy.

Until recently most authorities have agreed that the principal and perhaps only effect of anticoagulants is the limitation of clot formation and extension by interference with the clotting mechanism. Since the significant work of Wright [13] on the recanalization effect of anticoagulants, this view may require revision. While her work was done on fresh experimental thrombi, it suggests an important lytic action on firm clots, and such action may, in part, account for the improvement in the vision of the long-involved eye in this case.

In this group, three attacks had a sudden and four a slow onset.

In the group of poor results the interval between the onset of the occlusion and the initiation of therapy varied in duration more than in the first two groups. There was also a greater frequency of severe systemic disease, viz., systemic hypertension, diabetes, and generalized arteriosclerosis, and consequently more severe retinal arteriolar and angiosclerosis. Two of the patients had branch occlusions in the other eye.

The poor visual result was due to lack of absorption of a massive macular hemorrhage in three patients, to macular hole formation from traction of fibrous strands in one, and to extensive scarring in the macular region in five, all findings pointing to a greater disturbance of the absorptive mechanisms than was encountered in the first two groups.

Among the poor results there was only one occlusion with sudden, and one with rapid (within 24 hours), onset. Six attacks developed slowly.

The group of five failures includes one patient with bilateral occlusion of the central vein of two years and one month's duration, whose vision at the beginning of therapy was nil in one eye and light perception in the other.

The intervals between onset of the occlusion and initiation of therapy were relatively short in this group, varying from four days to four weeks, with the above-mentioned exception. The two patients with the shortest intervals had a severe systemic disease, diabetes with hypertension and generalized arteriosclerosis, respectively. The fourth patient had an essential hypertension of short duration, only mild retinal angiosclerosis in the fellow eye, and a long period of prodromal symptoms with visible collateral formation at the time of occlusion. Focal arteriolar spasms and several areas of postspastic sclerosis were specially noted in the eye with the occlusion, suggesting local reflex spasms, since such findings were absent in the other eye. This patient was followed only for a short period, during which the vision of 1/200 did not improve. Prolonged anticoagulant administration, perhaps combined with retrobulbar injections of an antispasmodic, might have produced a more favorable outcome, similar to that in Cases 27 and 46.

In the group of failures the onset of the occlusion was rapid (within two days) in one and slow in the remaining four.

2. Incomplete Occlusions of the Central Vein

The visual end-results in the incomplete occlusions of the central vein were good in three patients and fair in five.

The interval between onset of the occlusion and initiation of anticoagulant therapy was short in two and unknown in one of the patients with good results. In all three of them the onset of the occlusion was sudden.

In this group the intervals varied from two days to two years and there were three sudden and two slow onsets of the occlusion.

In our series, the good and fair results in the incomplete occlusions of the central vein, and the deciding factors responsible for them, run parallel to those of the complete occlusions, although the over-all results are slightly better, lacking poor results and failures.

3. Main Branch Occlusions

Among the 14 main branch occlusions there were 11 good and 2 poor results and 1 failure. The two poor visual results were due to macular scarring. Among

the occlusions with good results seven had a sudden and four a slow onset. Among the latter, there were two eyes with formation of visible patent collaterals at the end of six and eight months, respectively.

4. Occlusions of Smaller Tributaries

Occlusions of these smaller venous branches responded with good results in four cases and with fair results in two. The inferior results in these two cases were due to scar formation in the macular region.

5. Imminent Venous Occlusions

Since recognition of the danger signals of an imminent occlusion at the earliest possible time is of paramount importance in its prevention, I shall briefly enumerate the most helpful findings, which have been discussed in detail elsewhere (Klien [11]).

The subjective symptoms may vary from a slight gradual reduction of central vision for which no apparent cause can be found to a more pronounced gradual failure of vision with small relative or absolute paracentral scotomas (Cases 12 and 15). Visual obscurations during periods of drowsiness or a feeling of fullness in the head are common.

The objective signs of increasing embarrassment of venous circulation are engorgement of the venous tree or of parts of it, associated with edema of the corresponding sector of the optic disc or of the retina along the involved tributaries. Misinterpretation of these findings is possible in hypertensive patients unless both fundi are carefully studied.

One of the most helpful signs is the absence of physiologic venous pulsation in one eye or in one of the main branches, while it is lively in the other eye, or the other branch. If venous pulsation is normally absent, there may be a great difference in the ease with which it may be elicited in the two eyes by pressure upon them.

Neovascularisation, or dilatation and increasing tortuosity of preformed small vessels, on or near the disc is pathognomnic for an impairment of venous circulation of some duration.

The subjective and objective findings, enumerated above, are usually indications of a slowly developing occlusion, and their early recognition gives ample time to initiate preventive anticoagulant therapy.

Prevention of sudden occlusions calls for a different approach. An awareness of situations leading to stagnation in the retinal circulation is important. Most of the preventable sudden occlusions occur in patients with systemic diseases, and close cooperation between internist and ophthalmologist is necessary for any success in prophylactic treatment of these cases.

Of the 14 impending occlusions, 13 were prevented and preventive measures failed in 1. Eleven of the eyes in which the occlusion was prevented retained normal vision; the remaining two kept the impaired vision with central scotomas present at the onset of the treatment, although the objective signs of the imminent occlusion disappeared or improved. One of these two patients was observed only for a short time and may now belong to a group with either poorer or better results.

The one failure in this group occurred in a diabetic and hypertensive patient with bilateral involvement (Case 21).

One patient in this group (Case 12), a man 71 years of age with essential

hypertension, was first seen with diplopia caused by paresis of the left external rectus muscle, thought to have been due to a cerebral thromboembolic process. The right vision was 0.6—3, the left 1:5—4, a difference of which the patient had not been aware. There was a small paracentral scotoma in the right field. Physiologic venous pulsation was absent in the right eye and lively in the left; otherwise the fundi were similar, both revealing a moderate degree of retinal angiosclerosis. Anticoagulant therapy was started immediately and continued for six months. After five months the right vision had improved to 1.0+2, the visual field defect had disappeared and in the R. E. physiologic venous pulsation had returned. Also, the diplopia had disappeared.

A high percentage of the patients with impending occlusion had bilateral involvement: Three patients had a complete occlusion in the other eye; one had a main branch occlusion, and one had an imminent occlusion also in the other eye.

In three patients of this group the imminent occlusion was the second attack in the same eye, and in another one it was the third recurrent attack in the same vessel.

These facts show that impending occlusions are detected more easily in patients already under observation and alerted to note minor visual disturbances. Only in three patients was discovery of the imminent occlusion incidental.

In all these patients, with the one exception mentioned above, anticoagulants were administered over long periods (in two patients, 8 and 5 years, respectively; in two other patients, 3 years; in one, 14 months, and in the remaining patients from 3 months to 11 months).

The interval between the detection of the first subjective or objective premonitory symptoms and initiation of the prophylactic therapy were unknown in five patients because of lack of subjective symptoms; in the remaining patients it varied from three days to nine months. Two of the longest intervals were found in patients with perfect results; in one of them the first sign of a collateral pathway could be detected at the onset of therapy. In the one failure the interval was two weeks.

6. Bilateral Occlusions

Among the eight patients with bilateral involvement the better visual result was in the more recently affected eye, with the above-discussed exception (Case 21), in which the eye with an untreated occlusion of two year's duration regained useful vision while the imminent occlusion in the other eye, treated one month after the first symptoms were noted, was a complete therapeutic failure, necessitating enucleation within a short time.

All patients with bilateral occlusions suffered from the severer degrees of systemic diseases—two from essential hypertension, two from diabetes, and four, ranging in ages between 71 and 74, from marked generalized arteriosclerosis.

The following Tabulation indicates the degree of occlusion in each of these eyes and the respective visual end-results:

Number of Patients	Both Good Results	Both Fair Results	Both Poor Results	Both Failures
3	R = = L	R = = L		R — — L
2			— Y R — = L	
	Fair and Good	Poor and Good	Nil and Fair	
3	R — = L	R = = L	R = — L	

The tabulation shows that there were seven imminent occlusions in this group.

7. Recurrent Occlusions

Among the four patients with recurrent attacks in the same eye there were six good results in three patients and one good result and one failure in the fourth patient. The second occlusion in this patient occurred two weeks after anticoagulant therapy was terminated, four and a half months after the first occlusion (Case 51). Continuation of anticoagulant therapy in this patient with marked thrombotic tendencies not only might have prevented the second occlusion but also might have prolonged her life, since death occurred from coronary occlusion within two months of the termination of therapy. The following Tabulation illustrates the degree of occlusion in this group and the visual results:

Number of Patients	Good Results in Both Attacks	One Good result, One Failure
2	R — — L Y Y	
1		R Y Y L
	Good results in 3 Attacks	
1	R = = L =	

8. Venous Occlusions During Anticoagulant Therapy

Study of the group of four patients (Cases 6, 14, 30, 53) with venous occlusions during anticoagulant therapy shows a probably more than incidental connection between the prothrombin level and the therapeutic failure.

In Case 6, with low blood pressure and six weeks of arterial spasms preceding the occlusion of the central vein, stabilization at a therapeutic prothrombin level was difficult. Study of the laboratory data revealed that during the five months of anticoagulant therapy the prothrombin level was below 30% only three times.

Case 14 was first seen with an incomplete occlusion of the central vein and a visual acuity of 0.1, which was retained during the first four months of anticoagulant therapy. After this period, vision began to deteriorate rapidly, and the laboratory data covering the critical period indicated that stablilization of the prothrombin level had become difficult. Heparin was given at that time for a few days before continuation, for an eight months' period, with the original anticoagulant (phenindione). Complete occlusion was not prevented, and after two years vision was 2/200, but with good peripheral field and absence of glaucoma. An imminent main branch occlusion in the other eye was, however, prevented, and normal vision in this eye was preserved.

Case 30 had a similar course. When the patient was first seen, there was an incomplete occlusion of the central vein and vision of 0.4; the vision improved slightly during the first three and one-half months of therapy, then rapidly diminished to hand movement during the following two weeks. The laboratory data revealed that after a two-and-one-half-months' initial period of good prothrombin stabilization at therapeutic levels, a two-and-one-half-month period followed during which prothrombin levels reached 70% and were above therapeutic levels most of the time. The loss of the original visual improvement began during this latter period, and the occlusion became complete. The visual result after two years was 3/200 owing to macular scarring. The peripheral field was normal, and there was no glaucoma.

Case 53, a severely diabetic patient, suffered an occlusion of the right superior

main venous branch, which was preceded by a sudden occlusion of the corresponding superior arterial branch, a typical example of a stagnation thrombosis. This event took place while the patient was on anticoagulant therapy for coronary artery disease. The prothrombin level was, however, kept at 40% (one-stage method). Within three weeks of the venous occlusion physiologic venous pulsation was again visible in the affected branch, but a massive macular hemorrhage had reduced vision to 3/200. In the fellow eye there was during this time, for about six weeks, marked venous congestion and complete absence of physiologic pulsation, while the vision remained 1.5.

Physiologic pulsation of the superior main venous branch returned in the left eye, with lessening of venous congestion, while the patient was still on anticoagulant therapy. This therapy was terminated when a severe intestinal hemorrhage occurred for which no cause could be found (prothrombin level at 68%, one-stage method).

During this hemorrhagic period the left vision blacked out completely for a day. Ophthalmoscopic examination a day later revealed narrow left retinal arteries and sludging of the blood column in all inferior venous branches. Vision had improved to 0.8. Several days later the arteries had normal caliber again; the sludging of the blood had disappeared, and vision was 1.2.

This patient surely is likely to have future retinal venous occlusions with a large element of hemodynamic disturbances in their pathogenesis.

All four patients of this group have in common an "escape" from therapeutic prothrombin levels at the time of the venous occlusions.

Two of them had unmistakable evidence of stagnation in their retinal circulation, caused by arterial spasms. One wonders if antispasmodics should not be added to the anticoagulants in these cases, to be given systemically in cases of bilateral arterial spasms and locally, as retrobulbar injection, in the unilateral cases of reflex vasoconstriction.

Comment

A. *The Onset of Venous Occlusions.*—Among the complete and incomplete occlusions of the central vein and the main branch occlusion, all of which have a more complex pathogenesis than the smaller branch occlusions, there were 21 occlusions with sudden onset, 2 with rapid onset (within a few days), and 25 with slow onset.

In scanning the therapeutic results in these three categories, one finds that the number of sudden onsets is higher in occlusions with good results and diminishes proportionately in the fair and poor results in favor of slow onsets. Among the good results with a slow onset of the occlusion there was a remarkable frequency of patient collateral pathways, either directly visible or indicated by a characteristic clinical course of the recovery period (Cases 18, 27, 28, 39, 46). 39, 46).

One gains the impression that a slow onset of the occlusion might be more favorable for eyes with preformed serviceable collaterals, and unfavorable for eyes without them, because of the relentlessly progressive nature of the lesions which produce occlusions with slow onsets, such as primary degenerative venous disease and sclerotic compression.

Occlusions with a sudden onset, suggesting a large element of stagnation in their mechanism and thus a somewhat reversible element, might respond better

to anticoagulant therapy, in general, also, in those patients who lack the defense of a collateral pathway.

The following Tabulation shows the type of onset and the respective results in the complete and incomplete occlusions of the central vein and of main branches:

Type of Occlusion	Visual Result	Cases, No.		
		Sudden Onset	Rapid Onset	Slow Onset
—	Good	3		2
—	Fair	3		4
—	Poor	1		6
—	Nil		1	4
=	Good	3		
=	Fair	3		2
Y	Good	7		4
Y	Poor	1		1
Y	Nil	1		

There is also the fact to be taken into consideration that a sudden onset is more alarming to the patient and medical advice is sought earlier, thus shortening the interval between occlusion and onset of therapy.

B. *The Interval Between Occlusion and Initiation of Therapy.*—While it must be agreed upon that a short interval is desirable, it is by no means essential in all cases for a good therapeutic result. It is true that in the occlusions with good results, especially those with sudden onsets, the intervals were usually short.

However, in the group of fair and poor results, with a majority of longer intervals, residual macular damage was responsible for the lowered central visual acuity. All of these patients retained a good peripheral field. These facts modify the first impression that the interval is all-important. It seems that the benefit of a short interval lies particularly in a greater speed of absorption of retinal hemorrhages and other debris, and therefore of more rapid rectification of nutritional disturbances and anoxia, thus resulting in a reduced size and number of retinal scars.

C. *Results.*—One of the most interesting features in the recovery of venous occlusions is the speed with which good or fair therapeutic results are obtained under similar circumstances, such as the site of occlusion, the amount of hemorrhage, etc. In some occlusions the maximum good or fair result has been accomplished after a few weeks or sometimes even days; in others, months or years are required. The latter have a fairly typical course of their recovery period. First, vision improves only slightly, or is perhaps only stabilized at the initial amount. This period may last for weeks or months; then further slight improvement occurs. After several such periods of slow improvement within one to three years, normal vision may be regained (Cases 27 and 46 are typical of this course). These patients develop an efficient collateral pathway.

The former group, with rapid recovery, probably comprises those patients in whom a short period of heparinization may be as good as more prolonged anticoagulant therapy. It stands to reason that recovery in these patients is brought about by partial or complete reopening of the original pathway. Careful scrutiny of the systemic condition of these patients is necessary to guard against

conditions which might lead to hemodynamic disturbances in the retinal circulation and to repeat a short-term anticoagulant treatment if such conditions develop (Case 16 may be characteristic of this type).

No direct connection has been found in our series between reestablishment of the venous circulation in one form or another and an existing systemic disease. The visual results, however, may well be influenced by such coexisting diseases, which render the absorptive mechanisms in the eye less effective even before an occlusion has developed.

It is noteworthy that in some cases marked improvement of the vision in the other eye occurred (Cases 11, 15, 23, 37, 42, 46, 49). The greatest increase in vision was from 0.5 to 1.0, in a patient whose treatment of the eye with the occlusion was a complete failure. The most surprising benefit to the vision of the eye was encountered in a patient with incipient cataracts, whose corrected vision of 0.3 in the other eye was thought to be due to the cataract but which improved to 0.6 within a year.

D. *Pathogenesis.*—Our knowledge of the three mechanisms of the occlusion of the central vein and its main tributaries gained from the study of histopathological material, viz., occlusion by external compression with secondary endothelial damage; occlusion by primary venous disease, either degenerative or inflammatory, and occlusion by stagnation thrombosis, is not easily applied to clinical material. The fact that none of these mechanisms occurs in a pure form in these occlusions and each only predominates over one or two of the other factors complicates matters.

While sclerotic compression and primary venous disease may be recognized in the histologic material without great difficulty, it is almost impossible to make the clinical differentiation between these two with our present knowledge. There is only one finding which promises to be of aid when we have learned how to interpret it by paying close attention to it and to the circumstances under which it is present, namely, a unilateral narrowing of the arterial tree in the eye with the occlusion. In our series it was found in nine patients. In two of them there was marked retinal arteriolar sclerosis in the other eye, and the narrowing was suspected to be due to an atheroma of the central artery. In one of these two there was also a retraction of the bifurcation of the central artery (Case 30). In the remaining seven patients the vessels in the other eye were either normal or only mildly sclerotic. In these the narrowing may have been due to reflex vasoconstriction, which is more likely to be found in intimal irritation from primary venous disease (Cases 10, 16, 24, 35).

The peculiar appearance of the fundus with extensive whitish discoloration, discussed in Part I, which was found in three patients (two of which lost the eye and made histopathologic examination possible), should also be mentioned as a possible sign of primary venous disease, inflammatory type (Cases 1, 55-1, and 55-6).

Otherwise, both types have a slow onset, as a rule.

The third mechanism of occlusion, that of stagnation, which is diagnosed histologically mainly by absence of occlusive degrees of lesions characteristic of the other two mechanisms and by a carefully taken history, has a more definite clinical picture. Its onset is usually sudden; its recovery under anticoagulant therapy is often rapid, and we know of many causes of hemodynamic disturbances in the retinal circulation, viz., sudden reduction of blood pressure in hypertensive

patients, spastic hypertensive episodes, cardiac decompensation, severe loss of blood, surgical procedures, cranial fractures, severe falls with shock, blood dyscrasias, marasmus and low blood pressure in senility, and an angioneurotic constitution. Many of these conditions were present in some of the patients of our series.

Analysis of the subjective and objective clinical symptoms of an occlusion, which may suggest which of the occlusive mechanisms is the predominant one, may aid in the prognostic evaluation of the case and in the choice of therapy.

It may guard against too early a dismissal from observation of a patient with rapid recovery under a short-term anticoagulant treatment, or it may suggest the addition of an antispasmodic to the therapy. It also may ward off discouragement in patients and physicians when no immediate response to therapy occurs.

Sclerotic compression and primary venous disease of the degenerative type call for long-term or life-long anticoagulant therapy. The principal aims of this therapy are the reduction of stress upon the vessel wall to permit as much repair of damaged endothelium as possible, to keep a small opening in the original pathway open as long as possible to gain time for efficient collateral formation, and, finally, to lessen the danger of secondary thrombus formation at the site of the damaged vessel wall.

Occlusions with a large element of stagnation in their pathogenesis may do well with a short period of heparinization, to be repeated whenever the cause for stagnation recurs.

E. *Complications of Anticoagulant Therapy.*—Hematuria developed in seven patients. In three of these the therapy was continued after the proper prothrombin level had been reached again; in others therapy of considerable duration had already given the desired results at the time of the complication. Other complications were a prolonged attack of epistaxis in one patient after 1 year of therapy and an intestinal hemorrhage in another patient after 11 months of therapy.

There was one death from cerebral hemorrhage which was considered possibly due to the anticoagulant. This severely hypertensive patient (Case 35) had developed an occlusion of the right central vein during a period of markedly lowered blood pressure (148/90). At the time of her death the blood pressure had risen to 220/120 again, an event which could produce a cerebral hemorrhage even without anticoagulant effect.

F. *Types of Anticoagulants and Methods of Control.*—Since the treatment of a large number of the patients in this series was carried out or, at least, begun before the general use of any prothrombin depressant other than bishydroxycoumarin (Dicumarol), this drug was used more frequently than any of the others. As newer drugs came along certain ones, namely ethyl biscoumacetate (Tromexan ethyl acetate), phenindione, and diphenadione (Dipaxin), were administered. Each drug has its own properties, advantages, and disadvantages.‡ There is fairly general agreement that thromboembolism or hemorrhage rarely occurs when the prothrombin remains between 10% and 30% of normal—the therapeutic bracket. This has been true in our own experience, and we have observed a number of episodes of thrombosis and/or embolism during periods of "escape" above 30%. It has been our experience that the danger from too much clotting is greater than the bleeding hazard, and, in general, we prefer to keep a patient's prothrombin between 10% and 20% rather than between

‡ References 1-5.

20% and 30%. A drug providing slow induction and moderately slow recovery, such as bishydroxycoumarin, provides for less easily controlled prothrombin levels than one which brings about rapid induction and slow recovery, such as diphenadione.[1] In the case of drugs with rapid induction and rapid recovery (ethyl biscoumacetate and phenindione) one must be especially alert to avoid periods of "escape" from therapeutic levels. During such periods of "escape" the prothrombin depressant should be supplemented by intermittent injections of heparin. The importance of continuous, complete control is well illustrated in the four disappointing failures in this series in patients who ordinarily might have expected good results.

Patients who were seen in the first days after the onset of the occlusion were treated immediately with heparin, which was continued (intravenously every four hours) until the prothrombin depressant became effective. It is particularly important that patients who are seen early be controlled immediately, and heparin is the only satisfactory drug providing such immediate control. If the patient is to be given a prothrombin depressant, heparin must be used intravenously, since it influences the prothrombin level. When given by this method it is excreted rapidly and its effect has disappeared in practically all instances at the end of six hours. Prothrombin levels were controlled by the two-stage prothrombin assay. It is technically a more involved procedure but is a considerably more accurate assay than the more commonly used one-stage method. Many patients will be satisfactorily controlled over a period of time with the one-stage test, but an occasional erroneous result may be serious.[1] Recently in our laboratory eight different thromboplastin preparations, five of them available commercially, were used in the one-stage technique to measure the prothrombin levels. With use of the same techniques on the same plasma but with different thromboplastin preparations results varied over a range of 90%.§ It is such variation that makes it difficult to compare data from one laboratory with those of others and is responsible for much of the confusion in the anticoagulant field today. Until a method more reliable than the one-stage and less involved than the two-stage is available such confusion will continue.

Recently, the discovery by Troll and Sherry[6] that the synthetic substrate *p*-toluenesulfonylarginine methyl ester (TAME) interacts with thrombin to release free arginine carboxyl groups titratable with any standard alkali offers for the first time a chemical method for the measure of thrombin. On this principle the so-called TAME method for prothrombin determination was developed and in patients on anticoagulant therapy was found to parallel satisfactorily the two-stage method.‖ The technique is considerably less involved than that of the two-stage test and may prove to be the answer to the problem of accurate control of anticoagulant therapy.

Summary and Conclusions

The first part of this paper deals with the histopathologic analysis of 18 eyes lost from secondary glaucoma after occlusion of the central retinal vein and of 3 eyes with imminent venous occlusions.

Three different occlusive mechanisms could be demonstrated: (1) occlusion by external compression and secondary endothelial proliferation; (2) occlusion by primary venous disease, either degenerative or inflammatory in nature, and

§ Arscott, P. M.; Koppel, L. J., and Olwin, J. H.: Unpublished data.

‖ Reference 7. Arscott, P. M.; Koppel, L. J., and Olwin, J. H.: Unpublished data.

(3) occlusion by stagnation thrombosis. The pertinent features of the clinical histories and medical findings are discussed in relation to these histopathologic conditions.

The second part of the survey offers some interesting observations concerning the therapeutic results in 53 patients with venous retinal occlusions, although it is recognized that the sample (57 occlusions) is too small to warrant any final conclusions; moreover, because it is obviously not possible to withold therapy, there can be no control series.

Briefly, our therapeutic results in the complete and incomplete occlusions of the central vein or of a main branch were good (vision 0.6 to 1.2) in 18 occlusions (32.7%). The over-all good, fair, and poor results with preservation of peripheral vision were obtained in 41 occlusions (74.5%). Vision from 0.1 to 1.2 was regained in 30 patients (54.5%). There were three enucleations for uncontrolled secondary glaucoma (5.4%).

It appears that for recovery from an already established occlusion of the central vein or its main tributaries there has to be a combination of at least two of several favorable circumstances, as follows: (1) a short interval between onset of the occlusion and initiation of anticoagulant therapy, and/or (2) a large reversible element in the pathogenesis of the occlusion, such as originates in hemodynamic disturbances of various kinds, and/or (3) favorable topographic relationships with neighboring vascular systems such as the ciliary and vaginal vessels, facilitating the development of effective collateral pathways. For good central vision, in addition to preservation of the eyeball and of peripheral vision, fair general health with normally functioning ocular absorptive mechanisms to reduce residual lesions may be added as a fourth favorable feature. Occlusions with a large element of stagnation in their pathogenesis should be treated with an antispasmodic in addition to the anticoagulant. Tolazoline (Priscoline) given orally or as retrobulbar injection appears to be of benefit.

The best use of anticoagulant therapy in retinal venous occlusions would be the prophylactic use, as illustrated by the favorable results in 14 imminent occlusions treated in this series.

As pointed out by one of us (J. O.), in the last paragraph of this paper, long-term anticoagulant therapy calls for extreme vigilance for "escapes" from the desired therapeutic level, not only into dangerously low prothrombin levels but also into the higher ineffective bracket.

TABLE 1.—*Occlusion of Central Retinal Vein: Histopathologic Cases, Mainly Stagnation Type*

Case	Sex	Age, Yr.	B.P. & Systemic Disease	Site	Onset	Other Eye	Onset of Glaucoma	Interval From Onset to Occl. Therapy	Therapy	Type of Occlusion
36-13	M	71	130/80	R.C.V. R.V.=L.P.	Sudden, overnight	L.V. 1.0, II degree retinal angiosclerosis	4 wk.			Stagnation type, collapse of main branch, element of primary venous disease (degenerative)
32-21	F	41	235/125	L.C.V., Large retinal hemorrhages, some vitreous haze	Slow, intermittent blurring	R.V. 1.5, generalized spastic contraction of arterioles, a few areas of postspastic sclerosis	6 mo.			Stagnation type, sclerotic compression of branches, no compression of central vein
33-48	F	56	300/140 240/92 Enlarged L. heart	R.C.V.	Sudden	L.V. normal, marked generalized arteriolar narrowing, I degree arteriolar sclerosis	4 mo.			Stagnation type, element of primary venous disease (degenerative), no compression of vein

TABLE 2.—*Occlusion of Central Retinal Vein: Histopathologic Cases, Mainly Sclerotic Compression Type*

Case	Sex	Age, Yr.	B.P. & Systemic Disease	Site	Onset	Other Eye	Onset of Glaucoma	Interval From Onset to Occl. Therapy	Therapy	Type of Occlusion
30-17	M	63	220/110, diabetes	L.C.V. L.V.=L.P. Massive retinal hemorrhage	Sudden	R.V. 8/200, diabetic retinopathy, Grade III	3½ mo. after occlusion			Sclerotic compression type, element of primary venous disease (degenerative)
40-20	F	61	140/90, diabetes	R.C.V., massive hemorrhage in vitreous	Sudden	L.V. 1.0, no retinopathy, vessels normal	4 days after occlusion			Sclerotic compression type, element of primary venous disease (degenerative)
33-33	M	54	170/110	L.C.V., massive vitreous hemorrhage	Within a few days	R.V. 1.5, vessels normal	5 days after occl.			Sclerotic compression type
38-30	F	54	158/100	L.C.V., serpiginous ulcer	Slow, within 6 mo.	R.V. 1.0, normal retinal vessels	6 mo.			Sclerotic compression type, unfavorable anatomic relations, good collaterals
	M	72	130/80	L.C.V., vitreous hemorrhage	Slow, prodromal signs 2 yr.	R.V. normal, I degree retinal angiosclerosis	4 days			Sclerotic compression type
34-17	F	66	180/100	L.C.V.	Sudden	R.V. normal	12 mo.			Sclerotic compression type, good collaterals
40-22	M	70	160/95	Imminent L.C.V., subluxation of R. lens, intermittent sec., glaucoma		R.V. normal, I degree retinal angiosclerosis	Present before occlusion, subluxation of lens			Sclerotic compression type
40-14	F	62	170/92, diabetes, arteriosclerosis	Imminent L.C.V., diabetic retinopathy Grade IV, rubeosis iridis, secondary glaucoma		R.V. 10/200, diabetic retinopathy, Grade IV	Present before occlusion (rubeosis iridis)			Sclerotic compression type, element of primary venous disease (degenerative)
31-13	M	64	104/82	R.C.V., serpiginous ulcer	Sudden	L.V. 1.0, vessels normal	4½ mo.			Sclerotic compression type

TABLE 3.—*Occlusion of Central Retinal Vein: Histopathologic Cases, Mainly Primary Venous Disease Type*

Case	Sex	Age, Yr.	B.P. & Systemic Disease	Site	Onset	Other Eye	Onset of Glaucoma	Interval From Onset to Occl. Therapy	Therapy	Type of Occlusion
50-47	F	58	200/90, imminent cardiac failure, 150/90	R.C.V. R.V.=nil	Rapid, within 2 days	L.V. 1.0, I degree retinal arteriolar sclerosis	1 mo. after occlusion			Primary venous disease type (degenerative)
51-20	F	78	210/100, mild cardiac decompensation	R.C.V. R.V.=nil	Slow, within 2 mo.	L.V. 1.0	3 mo. after first blurring of vision			Primary venous disease type (degenerative)
52-8	F	61	Diabetes	R.C.V., massive retinal, no vitreous, hemorrhage	Slow	Diabetic retinopathy, B.E. for several years	Several months			Primary venous disease (degenerative)
	M	32	125/80, syphilis, L. maxillary sinusitis	L.C.V., massive retinal hemorrhages	Slow	R.V. normal, vessels normal	Several months			Primary venous disease (inflammatory)
	M	57	200/105	R.C.V., vitreous hemorrhage	Sudden	L.V. normal, vessels normal	4 wk.			Primary venous disease (degenerative) plus sclerotic compression
40-44	F	65	154/88, diabetes	Imminent R.C.V., R.V., H.M., diabetic retinopathy, rubeosis iridis, secondary glaucoma		L.V. 3/200, diabetic retinopathy, Grade III	Present before occlusion (rubeosis iridis)			Primary venous disease (degenerative), element of sclerotic compression
36-14	M	34	Normal	L.C.V., L.V. 6/200, massive retinal hemorrhages, some vitreous hemorrhage	Slow	R.V. 1.0, solitary chorioretinitis lesion (3 D.D.), some convolutions of new vessels on disc, a few small ret. hemorrhages near lesion	3 mo.			Primary venous disease type (inflammatory)
55-6	M	27	Normal, PPD skin test ++	R.C.V. at first incomplete; blurring 2 wk.; R.V. 0.5 down to L.P. within 2 wk., massive retin. hem., no vitreous hemorrhage	Slow, within 1 mo.	L.V. 1.0, normal vessels	4 mo. after occlusion	2 wk.	Bishydroxycoumarin 10 days acetazolea-mide	Primary venous disease (inflammatory), element of stagnation
55-1	F	51	150/70, arthritis, severe L. sinusitis, marked disseminated arteriosclerosis	L.C.V. incomplete at first, L.V. down to 3/200 within 7 mo.	Slow	R.V. 1.2, I degree retinal angiosclerosis	9 mo.	2 mo.	Typhoid, bishydroxycoumarin 3 wk. (severe hematuria), sup. cervical sympathectomy	Primary venous disease (inflammatory?), element of sclerotic compression

TABLE 4.—*Complete Occlusion of Central Vein: Good Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
1	M	56	125/75	I. Attack L.C.V. II. Attack L.C.V. 14 mo. after I.; I degree ret. angiosclerosis	Sudden Sudden	24 hr. 36 hr.	Heparin, bishydroxycoumarin 1 yr., 7½ yr. bishydroxycoumarin	R.V. 1.0 Normal fundus	None None	L. vision 1.0 L. vision 0.6 (incip. cataract)	After 5 yr. incipient cataract, L. vision 0.5
27	M	67	140/85, angina pectoris	L.C.V., L.V. 3/200, fundus obscured by vitreous haze	Sudden	6 mo.	Bishydroxycoumarin 10½ mo.	R.V. 0.8, I degree ret. angiosclerosis	Hematuria at prothrombin 3%, therapy resumed after control	L.V. 0.6 after 7 mo., 1.0 after 2 yr., sec. glaucoma after 5 mo. (controlled); L.V. still normal after 5 yr.	
30	F	68	210/110	L.C.V., L.V. 2/200, III degree ret. arteriolar sclerosis	Slow	1 wk.	Bishydroxycoumarin 5 mo.	R.V. 1.0, III degree ret arteriolar sclerosis	None	L.V. 0.8, many new vessels on L. disc	Death from ruptured cerebral aneurysm
46	M	48	140/90 150/88	R.C.V., R.V. 0.1	Slow, within 4 wk.	2 wk.	Heparin, bishydroxycoumarin 11 mo.	L.V. 1.0, I to II degree ret. arteriosclerosis	None	R.V. 0.6 after 2 mo., 1.0 after 3 yr.; L.V. 1.5, R. sec. glauc. (31.0) after 1 mo. (controlled), glaucoma disappeared after 13 mo.	

TABLE 5.—*Complete Occlusion of Central Vein: Fair Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
3	M	75	180/90	R.C.V., R.V. 0.1	Sudden, overnight after penicillin injection	2 mo.	Bishydroxycoumarin	L.V. 0.6	Hematuria after 3 wk. (prothrombin 8%), stopped after several days (prothrombin 47%), therapy continued	R.V. 0.1, large central scotoma, no glaucoma after 2 yr.	Compression type plus element of stagnation?
7	F	71	120/70	L.C.V., L.V. 0.6, 3/200, imminent R.C.V.	Slow	6 wk. after onset of prodromal symptoms	Ethyl biscoumacetate 1 mo., phenindione 3 wk.	R.V. 0.8, II degree retinal angiosclerosis	None	L.V. 0.1, large central scotoma, R.V. 1.5 after 4 wk., still normal after 5 yr.	Probably sclerotic compression type, element of stagnation?
21	F	67	208/96 192/102, diabetes	R.C.V., imminent L.C.V., R.V. 2/200, L.C.V. L.V., H.M.; new vessels on R. disc, II degree ret. angiosclerosis	Sudden, after a fall with fractured arm; sudden	2 yr. 2 wk.	Bishydroxycoumarin 4 mo.	L.V. 0.3, amblyopia ex anopsia, II degree ret. angiosclerosis	None	R.V.0.1, R. sec. glaucoma (controlled), L.V. H.M., sec. glaucoma, L. enucleation	Probably compression type, element of stagnation
35	F	50	148/90 220/120	R.C.V., R.V. 10/200	Slow	10 mo.	Bishydroxycoumarin 2 wk., ethyl biscoumacetate 10 days (interrupted for abdominal surgery), reinstated 4 wk.	L.V. 0.1 (amblyopic eye), I degree ret. arteriolar sclerosis	Cerebral hemorrhage after 4 wk., death; prothrombin 7.2% with 2-stage method, 22% with 1-stage method	R.V. 0.1 after 2 wk.	Probably primary venous disease plus element of stagnation
37	M	60	Diabetes	L.C.V., L.V. 0.1	Slow	8 mo.	Diphenadione 7 mo., discontinued for 2 ½ mo., reinstated 2 ½ mo.	R.V. 0.3 inc. cataract, no retinopathy	None	L.V. 0.1, no glaucoma, R.V. 0.6 −2 after 1 yr.	
42	M	80	130/85	R.C.V., R.V. 5/200, II degree ret. angiosclerosis	Sudden, after a fall	A few mo.	Diphenadione 17 mo.	L.V. 0.5, II degree ret. angiosclerosis	None	R.V. 0.3, small central scotoma, L.V. 0.8+3, no glaucoma after 2 yr.	

TABLE 5.—*Complete Occlusion of Central Vein: Fair Results (Continued)*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
52	M	55	250/144	L.C.V., L.V. 0.1, new vessels on L. disc, II to III degree arteriolar sclerosis	Slow, within 2 mo.	3 mo.	Bishyroxycoumarin 3 yr.	R.V. 1.5, II to III degree ret. arteriolar sclerosis, arterioles narrow B.E., physiologic ven. pulsation	None	L.V. 0.1, central scotoma, good collaterals, no physiol. ven. pulsation, no glaucoma after 3 yr.	

TABLE 6.—*Complete Occlusion of Central Vein: Poor Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
5	M	68	145/85, treated for L. sinus disease for several mo.	L.C.V., L.V. 3/200, hemorrhage and white discoloration of fundus, Schiøtz 23.0 23.0	Slow, within 2 wk.	1 mo.	Heparin, bishydroxycoumarin 1 mo.	R.V. 1.5, I incipient degree ret. angiosclerosis, Schiøtz 28.0	None	L.V. 10/200, large central scotoma, good periphery after 1 mo.	Probably compression type (atheroma C. artery), some primary venous disease (inflammatory)?
6	M	51	80/50	R.C.V. after 6 wk. of spasms of inf. arterial branch, R.V. 3/200, 12/200, 0.1, after 6 wk. 8/200	Slow	During anticoag. therapy for arterial occlusion	Bishydroxycoumarin 5 mo., stellate ganglion block, sodium thiosulfate i. v. twice a wk.	L.V. normal	None, not controlled, prothrombin level below 30% only 3 times in 5 mo.	No improvement of R. vision, vascular membrane on R. iris, incip. sec. glaucoma several wk. after venous occlusion	Probably stagnation type, plus?
23		75	210/104 300/142	R.C.V., R.V. 4/200, III degree ret. angiosclerosis	Slow, within 3 wk., with severe cold	3 wk.	Heparin, bishydroxycoumarin 9 days, bishydroxycoumarin 21 mo.	L.V. 0.8 – 1, III degree ret. angiosclerosis	Prothrombin 2% after 9 days, blue spot at ankle, therapy reinstated	R. V. 12/200, glaucoma after 3 mo. (controlled), L.V. improved to 1.2 – 3	Probably compression type
30	F	44	210/110 before therapy, severe headaches	L.C.V. at first incomplete, L.V. 0.4, after 4 mo. H.M. in spite of therapy, L. retinal arterioles narrower than R.	Slow, within 4 mo., prothrombin % above therapeutic level	Less than 2 mo. level 2 ½	Ethyl biscoumacetate, bishyroxycoumarin (better control) 1 yr., prothrombin above therapeutic level 2½ to 4 ½ mo. after initiation of therapy	R. V. 1.5, III ret. arteriolar sclerosis	Prolonged epistaxis after 1 yr.	End-result L.V. 3/200, large central scotoma, no glaucoma after 2 yr., no headaches after therapy	Probably primary venous disease plus compression (atheroma C.A.)
14	F	63	210/110	L.C.V., L.V. 0.1, incomplete, becoming complete within 4 mo. in spite of therapy, arteries narrow	Slow	2 wk.	Phenindione 4½ mo., heparin, phenindione 8 mo.	R.V. 1.0, marked dilatation of sup. venous branches pressed upon by sclerotic artery (imminent occlusion)	None	L.V. 2/200, hole in macula from traction by retina proliferans, R. V. still 1.0 after 2 yr., less venous engorgement, no glaucoma	

TABLE 6.—*Complete Occlusion of Central Vein: Poor Results (Continued)*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
34	M	71	Several "heart attacks" 2 and 3 yr. ago	L.C.V., L.V. 3/200, R. sup. branch C.V., R.V. 4/200, many new veins on l. disc and upper fundus, scar in R. macula, white lines along veins, edema upper half R. disc, hemorrhage along sup. branches, down into macula	? Sudden	5 yr., 2 wk.	Bishydroxycoumarin 15 mo.	II degree ret. angiosclerosis, B.E.	None	R.V. 16/200, J.5 after 3 mo., same after 1 yr., L.V. 3/200, no J., spontaneous collaterals before therapy, no glaucoma; large paracentral scotoma R.E., central scotoma L.E.	Probably primary venous disease plus sclerotic compression
43	M	73	200/98	R.C.V., R.V. 6/200	Within 1 day	2 wk.	Heparin, bishydroxycoumarin 2 wk.	L.V. 1.0	None	No improvement after 2 wk.	
44	M	65	122/78, diabetes	L.C.V., L.V., H.M., massive retinal hemorrhages	Slow	3 wk.	Heparin, bishydroxycoumarin 1 mo.	R.V. 1.0, no retinopathy, I degree ret. angiosclerosis	None	End-result large paracentral scotoma, L.V. 3/200, no glaucoma after 6 mo.	Probably primary venous disease
47	M	74	140/78	L.C.V., L.V., L.P., imminent R.C.V., marked venous engorgement R.V. 3/200, central scotoma	Sudden Sudden	3 yr. 4 mo.	Bishydroxycoumarin 2 wk.		None	L.V. 6/200, R.V. 1/200	

TABLE 7.—*Complete Occlusion of Central Vein: Failures*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
10	M	49	178/118	L.C.V., many new vessels on disc, focal arteriolar spasms, postspastic sclerosis	Slow, prodrom. symptoms 1 yr.	1 wk.	Bishydroxycoumarin, nicotinic acid 2 wk.	0.6 (aphakia) I degree ret. angiosclerosis	None	No visual improvement after 2 wk., L.V. still 1/200	Probably primary venous disease type, element of stagnation?
31	F	72	190/110	L.C.V., R.C.V., L.V.=nil, R.V.=L.P.	Slow Slow	2 yr. 1 mo.	Heparin, bishydroxycoumarin 20 days	II degree ret. angiosclerosis B.E.	Hematuria, prothrombin 8%, control difficult	L.E. glaucoma, R.E. no glaucoma after 5 mo.; R.V., L.P.	Probably mostly sclerotic compression
38	F	55	200/100, 164/84, diabetes	L.C.V., incomplete, with L.V. 1/200 for 3 wk.	Slow	10 days	Bishydroxycoumarin 5 wk., tolazoline orally 3 mo.	R.V. 1.2, I degree ret. angiosclerosis	None	Occlusion complete after 3 wk. sec. glaucoma 4 wk. afterwards, L.V. nil, enucleation	
49	F	67	160/85	R.C.V., R.V. 3/200, vitreous haze	Within 3 days	4 days	Bishydroxycoumarin 3 mo.	L.V. 0.5, III degree ret. angiosclerosis	None	No improvement of R.V., L.V. 1.0 after 3 mos., sec. glaucoma after 3 mo., enucleation after 4 mo.	

TABLE 8.—*Incomplete Occlusion of Central Veni: Good Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
4	M	55	180/100	L.C.V., incomplete, II degree retinal arteriolar sclerosis, generalized arteriolar attenuation	Sudden		Heparin, bishydroxycoumarin 1 mo., lumbodorsal sympathectomy	R.V. 1.2, generalized attenuation of arterioles, II degree arteriolar sclerosis	None	L.V. 0.8	Probably stagnation type plus sclerotic compression or primary venous disease
41	M	41	130/88	L.C.V., incomplete, L.V. 0.1	Sudden	A few days	Bishydroxycoumarin 3 ½ wk., stopped 1 wk., bishydroxycoumarin 1 mo.	R.V. 1.0, I to II degree ret. angiosclerosis	Hematuria after 3 ½ wk., controlled after 5 days, therapy resumed	L.V. 0.3 after 3 days, rapid improvement to normal	
26	M	70	Diabetes	R.C.V., incomplete, R.V. 0.1	Sudden	17 days	Bishydroxycoumarin 7 mo.	L.V. 1.0, I degree ret. angiosclerosis	None	R.V. 0.8 after 1 yr., no glaucoma	

TABLE 9.—*Incomplete Occlusion of Central Vein: Fair Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
15	M	66	Good general health	R.C.V. (incomplete), I blurring 8 mo. ago, R.V. 0.6; after 4 wk., 0.1	Slow	9 mo. after onset of prodromal symptoms	Bishydroxycoumarin 6 wk.	L.V. 1.0, I degree ret. angiosclerosis	Hematuria after 6 wk., prothrombin levels checked elsewhere	R.V. 8/200 after 5 wk., 0.2 after 6 mo., marked irregularities of ret. veins, L.V. improved to 1.2	Probably primary venous disease type, element of compression?
25	F	55	132/90	L.C.V. incomplete, L.V. 2/200, positive central scotoma	Sudden	2 days	Heparin, bishydroxycoumarin 1 mo.	R.V. 1.0, II degree ret. angiosclerosis	None	Marked improvement, L. vision, in 10 days L.V. 0.3	
29	F	70	210/90	R.C.V. (incomplete), imminent L.C.V., R.V. 0.4 −2, L.V. 0.4	Slow Slow	2 yr. 1 mo.	Heparin, ethyl biscoumacetate 7 mo., bishydroxycoumarin 7 mo.	II degree ret. arteriolar sclerosis B.E.	Ethyl biscoumacetate dermatitis	R.V. 0.4, L.V. 0.4	Probably compression type
32	F	66	146/90	R.C.V. incomplete, R.V. 6/200, I degree ret. angiosclerosis	Sudden, 1 premonitory symptom 2 yr. before: "ball of fire"	2 wk.	Heparin, ethyl biscoumacetate 10 mo.	L.V. 1.0, chronic noncongestive glaucoma, Schiøtz R. 30, L. 23; I degree ret. angiosclerosis	None	R.V. 0.4 after 10 mo.	Probably sclerotic compression plus element of stagnation
48	M	67	146/90	R.C.V. (incomplete), R.V. 0.1, inf. artery narrow	Sudden	2 wk.	Bishydroxycoumarin 9 mo.	L.V. 1.2, vessels normal	None	R.V. 0.1 after 3 yr., no glaucoma	Compression type atheroma of inf. artery

TABLE 10.—*Main Branch Occlusions: Good Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
8	F	65	210/140, diabetes 12 yr.	L. inf. branch C.V., II degree ret. arteriolar sclerosis	Sudden	1 wk.	Bishyrdoxycoumarin 4 mo.	R.V. 1.0, II degree ret. arteriolar sclerosis, no retinopathy	None	Rapid improvement L.V. to normal	Probable primary venous disease plus element of compression
13	F	53	160/100	L. sup. branch C.V.	Slow	6 wk.	Bishydroxycoumarin 11 mo.		Hematuria after 11 mo. (prothr. 9%) stopped in 3 days (prothr. 42%)	L.V. restored to normal	Compression type
16	M	57	120/74, acute embolic cystitis 3 yr. ago	R. sup. branch C.V., arteries narrow, R.V. 0.3	Sudden, overnight	3 days	Heparin, bishydroxycoumarin 1 wk.	L.V. 1.0, ret. vessels normal	None	Rapid improvement R. vision to normal	Probably stagnation type, element of sclerotic compression?
18	M	64	142/88, thrombocytes 1,417, 320, generalized arteriosclerosis	I attack: L. sup. branch C.V., L.V. 0.8, peri-central scotoma; II. attack after 2 mo., L.V. 2/200; III. imminent, new venous loops in disc engorged, intermittent blurring	Slow	4 mo.	Heparin 1,564 mg.	R.V. 1.2, I degree ret. angiosclerosis	None	I attack: L.V. 1.2 after 1 wk., o.k. for 2 mo. II. attack: L.V. 1.2 after 5 days, o.k. for 5 mo. III. attack: L.V. 1.5 after a few days, o.k. for 10 yr., good collateral formation	Probably stagnation type plus large element of sclerotic compression
19	M	60	185/105, 130/80	R. inf. branch C.V., R.V. 0.6, II to III degree ret. angiosclerosis	Sudden	2 mo.	Heparin, bishydroxycoumarin 3 mo.	L.V. 1.2, II to III degree ret. angiosclerosis	None	R.V. still 0.6 after 9 mo., hemorrhages absorbed after 1 mo.	Probably compression type, element of stagnation?
20	M	62	142/85	L. inf. branch C.V., L. sup. branch C.V. incomplete	Sudden	4 days	Heparin, bishydroxycoumarin 16 days	R.V. 1.5, I degree ret. angiosclerosis B.E.	None	End-result L.V. 1.5	Probably compression type
24	F	63	?	R. inf. branch C.V., R.V. 0.6, arteries narrow 1:3	Sudden	2 wk.	Bishydroxycoumarin 2½ mo.	L.V. 0.8, I degree ret. angiosclerosis	None	R.V. 1.0 after 3 yr., new veins on R. disc	Probably compression type (atheroma C.A.)

TABLE 10.—*Main Branch Occlusions: Good Results (Continued)*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
28	F	58	220/140	L. sup. branch C.V., L.V. 0.1	Slow	1 mo.	Ethyl biscoumacetate 5 mo., also prophylactic for R.E.	R. V. 1.5, III ret. arteriolar sclerosis, unfavorable sup. temp. AV crossing	None	L.V. 0.6 after 3 mo., 0.8 after 7 mo., 3 new large venous loops on L. disc	Probably primary venous disease (degenerative) plus compression
45	M	57	192/112, cerebral VA. 4 yr. ago	R. sup. branch C.V., R.V. 20/300, II degree ret. angiosclerosis, unfavorable I. temp. sup.AV crossing	Sudden	5 mo.	Bishydroxycoumarin 6 mo.	L.V. 1.5, II degree ret. angiosclerosis, after 3 yr. III degree	None	R.V. 0.8 no recurrence within 3 yr., no glaucoma	
51	F	58	220/110, recently 138/80	I. attack: L. sup. branch C.V., L.V. 1.0 down to H.M. within 5 days; II. attack: L.V. H.M., III degree ret. arteriolar sclerosis, some endarteritis and periphlebitis	Slow Sudden	1 mo. During	Bishydroxycoumarin, ethyl biscoumacetate, alkavervir	R.V. 1.2, III degree ret. arteriolar sclerosis	None	I attack: L.V. 0.8 after 4 wk. o.k. for 4 mo.; II. attack: L.V., H.M., death within 2 mo. (heart failure)	Probably primary venous disease plus element of stagnation

TABLE 11.—*Main Branch Occlusions: Poor Results Plus Failures*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
34	M	71	Several "heart attacks" 2 and 3 yr. ago	L.C.V., L.V. 3/200, R. sup. branch C.V., R.V. 4/200, many new veins on L. disc and upper fundus, scar in R. macula, white lines along veins, edema upper half R. disc, hemorrhage along sup. branches, down into macula	? Sudden	5 yr. 2 wk.	Bishydroxycoumarin 15 mo.	II degree ret. angiosclerosis B.E.	None	R. V. 16/200, J.5 after 3 mo. same after 1 yr., L.V. 3/200, no J., spontaneous collaterals before therapy, no glaucoma, large paracentral scotoma R.E., central scotoma L.E.	Probably primary venous disease plus sclerotic compression
53	M	52	176/96 110/76, diabetes 20 yr., general arteriosclerosis	R. sup. branch C.V., preceded by occlusion sup. artery; diabetic retinopathy II grade; physiol. ven. pulsation after 3 wk., R.V. 1/200, imminent L. C.V.	Sudden	During therapy	Bishydroxycoumarin 11 mo., tolazoline orally	L.V. 1.5, diabetic retinopathy II grade, physiol. venous pulsation absent	Intestinal hemorrhage, prothrombin level 68% (one-stage method), temporary loss of L. vision for a few days, sludging of L. venous blood column	R. V. 3/200, central scotoma, no glaucoma after 8 mo., L.V. 1.5, phys. ven. pulsation sup. branch, L.C.V. restored after 2 mo.	Stagnation type, primary venous disease likely
51	F	58	220/110, recently 138/80	I. attack: L. sup. branch C.V., L.V. 1.0, down to H.M. within 5 days; II. attack: L.V. H.M.; III degree ret. arteriolar sclerosis, some endoarteritis and periphlebitis	Slow Sudden	1 mo. During therapy	Bishydroxycoumarin, ethyl biscoumacetate, alkavervir	R.V. 1.2, III degree ret. arteriolar sclerosis	None	I. attack: L.V. 0.8 after 4 wk. o.k. for 4 mo.; II. attack: L.V., H.M., death within 2 mo. (heart failure)	Probably primary venous disease plus element of stagnation

TABLE 12.—*Secondary Branch Occlusions: Good and Fair Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
2	F	54	190/90 160/90	R. sup. temp. branch, R.V. 1.5, pericentral scotoma touching fixation point	Slow	2 wk.	Diphenadione 3 mo., also prophylactic for L.E.	L.V. 1.5, II degree ret. angiosclerosis, unfavorable sup. temp. AV crossing	None	Vision both eyes still normal	Compression type
11	M	52	220/? 150/	Imminent L.C.V., L. sup. temp. branch occlusion, L.V. 0.3, J.6, physiol. venous pulse absent	Slow	1 wk.	Bishydroxycoumarin 6 wk. at therapeutic prothrombin levels, contin. for several mo. at prophylactic levels (50%)	R.V. 1.0, II to III degree ret. arteriolar sclerosis, physiol. venous pulse present	Hematuria after 6 wk. therapy continued at prophylactic levels	R.V. 1.2, L.V. 1.0, J.1, Return of L. physiol. venous pulsation	Probably compression type, element of stagnation?
40	F	63	180/110	L. inf. temp. vein, L.V. 15/200, III degree ret. angiosclerosis	Slow	5 wk.	Diphenadione	R.V. 0.6+3	None	L.V. 0.2 after 1 wk., 10/200 after 4 mo.	
17	M	45	210/140, generalized arteriosclerosis	R. inf. temp., R.V. 0.1	Sudden	3 days	Bishydroxycoumarin 3 mo.	R.V. 1.5, arteriosclerotic retinopathy	None	R.V. 0.6 after 7 mo.	Died from cerebral thrombosis within a year
22	F	49	200/110 190/90, toxemia of pregnancy 2 yr. ago	L. superior temporal branch, L.V. 0.1	Sudden	2 wk.	Bishydroxycoumarin 4 mo.	R.V. 1.5, II degree arteriolar sclerosis	None	Marked visual improvement 10 days	Compression type
33	F	51	150/90	L. sup. temp. branch, L.V. 0.3	Slow, within 3 wk.	2 wk.	Bishydroxycoumarin 9 mo.	R.V. 0.8, no visible ret. vascular changes	None	End-result, 0.1 macular scar, no glaucoma after 3 yr.	

TABLE 13.—*Imminent Occlusions of Central Vein: Prevented, Good Results*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
7	F	71	120/70, cerebral angio-sclerosis, transient diplopia 2 yr. ago, myocardial infarction recently	L.C.V., L.V. 0.6, 3/200, imminent R.C.V.	Slow	6 wk. after onset of prodromal symptoms	Ethyl biscoumacetate 1 mo., phenindione 3 wk.	R.V. 0.8, II degree retinal angio-sclerosis	None	L.V. 0.1, large central scotoma, R.V. 1.5 after 4 wk., still normal after 5 yr.	Probably sclerotic compression type, element of stagnation?
11	M	52	220/? 150/	Imminent L.C.V., L. sup. temp. branch occlusion, L.V. 0.3, J.6, physiol. venous pulse absent	Slow	1 wk.	Bishydroxycoumarin 6 wk. at therapeutic prothrombin levels, contin. for several mo. at prophylactic levels (50%)	R.V. 1.0, II to III degree ret. arteriolar sclerosis, physiol. venous pulse present	Hematuria after 6 wk., therapy continued at prophylactic levels	R.V. 1.2, L.V. 1.0, J.1, return of L. physiol. venous pulsation	Probably compression type, element of stagnation?
12	M	71	260/100	Diplopia, L. abducens paresis, R.V. 0.6 −3, small scotoma, no physiol. venous pulsation, II degree ret. angiosclerosis	Slow		Bishydroxycoumarin 6 mo.	L.V. 1.5, L. physiol. venous pulsation, II degree ret. angio-sclerosis	None	R.V. 1.0+2 after 5 mo., central scotoma disappeared, R. physiol. venous pulse returned	Probably sclerotic compression type
14	F	63	210/110 156/70	L.C.V., L.V. 0.1, incomplete, becoming complete within 4 mo. in spite of therapy, arteries narrow	Slow	2 wk.	Phenindione 4 ½ mo., heparin, phenindione 8 mo.	R.V. 1.0, marked dilatation of sup. venous branches, pressed upon by sclerotic artery (imminent occlusion)	None	L.V. 2/200, hole in macula from traction by retinitis proliferans, R.V. still 1.0 after 2 yr., less venous engorgement, no glaucoma	

TABLE 13.—*Imminent Occlusions of Central Vein: Prevented, Good Results (Continued)*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
18	M	64	142/88, thrombocytes 1,417,320 generalized arteriosclerosis	I. attack: L. sup. branch C.V., L.V. 0.8, pericentral scotoma; II. attack after 2 mo., L.V. 2/200; III. imminent, new venous loops in disc, engorged, intermittent blurring	Slow Slow Slow	4 mo. 3 days 3 days	Heparin 1564 mg. Heparin 2100 mg. Bishydroxycoumarin 5 yr.	R. V. 1.2, I degree ret. angiosclerosis	None	I attack: L.V. 1.2 after 1 wk., o.k. for 2 mo.; II. attack: L.V. 1.2 after 5 days, o.k. for 5 mo.; III. attack: L.V. 1.5 after a few days, o.k. for 10 yr., good collateral formation	Probably stagnation type plus large element of sclerotic compression
36	F	62	200/100 160/90	Imminent R. C.V., R.V. 0.6, II degree ret. angiosclerosis, tremendous venous engorgement, edema of discs	Slow, intermittent blurring 7 mo.	9 mo.	Bishydroxycoumarin 8 yr., lumboloxal sympathectomy	L.V. 1/200, hole in macula, contusion 25 yr. ago, II degree ret. angiosclerosis, marked venous engorgement	None	R.V. 0.8 after 5 mo., 1.2+3 after 2 yr. for 6 yr. (to date), good collateral formation	Probably mostly compression type, element of stagnation?
40	F	70	210/90	R.C.V. (incomplete), imminent L.C.V., R.V. 0.4 −2, L.V. 0.4	Slow Slow	2 yr. 1 mo.	Heparin, ethyl biscoumacetate 7 mo., bishydroxycoumarin 7 mo.	II degree ret. arteriolar sclerosis B.E.	Ethyl biscoumacetate dermatitis	R.V. 0.4, L.V. 0.4	Probably compression type
47	M	74	140/80	Imminent R.C.V., R.V. 0.8; L.C.V., L.V. 0.8.; Imminent R.C.V., acute attack of glaucoma R.E. 1 mo. prior to 1st visit	Slow Slow	2 mo. after 1st symptoms	Bishydroxycoumarin 8 mo., interval 5 mo. ethyl biscoumacetate 4 mo., interval 8 mo., ethyl biscoumacetate 2 yr., all therapy prophylactic	III degree ret. angiosclerosis B.E.	None	R.+L.V. 0.8, disappearance of venous congestion, glaucoma controlled reappearance R. venous congestion, R.V. 0.8 −3, after 3 yr. R.V. 0.4, L.V. 0.8	

TABLE 13.—*Imminent Occlusions of Central Vein: Prevented, Good Results (Continued)*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
50	M	66	140/85	Imminent L. C.V., L.V. 0.8, marked venous engorgement	Slow	6 mo.	Bishydroxycoumarin 3 mo., bishydroxycoumarin after 2 mo. interval 3 yr. (up to present)	R.V. 1.2, II degree ret. angiosclerosis	None	L.V. 1.0 after 3 mo., down again to 0.8; after resumption of therapy up to 1.0, fluctuates now between 0.6 and 0.8	Probably sclerotic compression
53	M	52	176/96 110/70, diabetes 20 years, general arteriosclerosis	R. sup. branch C.V., preceded by occlusion sup. artery, diabetic retinopathy II grade, physiol. ven. pulsation after 3 wk., R.V. 1/200, imminent L. C.V.	Sudden	During therapy	Bishydroxycoumarin 11 mo., tolazoline orally	L.V. 1.5, diabetic retinopathy II grade, Physiol. venous pulsation absent	Intestinal hemorrhage, prothrombin level 68% (one-stage method), temporary loss of L. vision for a few days, sludging of L. venous blood column	R.V. 3/200, central scotoma, no glaucoma after 8 mo., L.V. 1.5, phys. ven. pulsation sup. branch L.C.V. restored after 2 mo.	Stagnation type, primary venous disease likely

TABLE 14.—*Imminent Occlusions of Central Vein: Fair and Poor Results and Not Prevented*

Case	Sex	Age	B.P. & Systemic Disease	Site of Occlusion	Onset	Interval from Onset to Therapy	Therapy	Other Eye	Complications of Anticoag. Therapy	Results	Remarks
29	F	70	210/90	R.C.V. (incomplete), imminent L.C.V., R.V. 0.4 −2, L.V. 0.4	Slow Slow	2 yr. 1 mo.	Heparin, ethyl biscoumacetate 7 mo., bishydroxycoumarin 7 mo.	II degree ret. arteriolar sclerosis B.E	Ethyl biscoumacetate dermatitis	R.V. 0.4, L.V. 0.4	Probably compression type
47	M	74	140/78	L.C.V., L.V., L.P., imminent R.C.V., marked venous engorgement, R.V. 3/200, central scotoma	Sudden Sudden	3 yr. 4 mo.	Bishydroxycoumarin 2 wk.		None	L.V. 6/200, R.V. 1/200	
21	F	67	208/96 192/102, diabetes	R.C.V., imminent L.C.V., R.V. 2/200, L.C.V., L.V., H.M., new vessels on R. disc, II degree ret. angiosclerosis	Sudden, after a fall with fractured arm; sudden	2 yr. 2 wk.	Bishydroxycoumarin 4 mo.	L.V. 0.3, amblyopia ex anopsia, II degree ret. angiosclerosis	None	R.V. 0.1, R. sec. glaucoma (controlled), L.V., H.M., sec. glaucoma, L. enucleation	Probably compression type

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Retrobulbar Air Injection with Planigraphy

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All too frequently the ophthalmologist finds himself at a loss for adequate methods of diagnosis of orbital space-taking lesions. The effective treatment of such patients is greatly aided by the proper localization of the pathology. Various attempts have been made to localize orbital tumors more accurately or to confirm their presence. The exploration of any orbit presents many difficulties unless a definite tumor mass is palpable or routine neurological and x-ray examinations offer suggestions as to localization of the lesion. Even in such cases more exact localization and determination of the limits of extension of the lesion would be of value.

The introduction of a contrast medium into the orbit has been advocated by several investigators as a means of establishing the presence and location of space-occupying lesions. Criteria which should be satisfied in selecting a contrast medium include the following: (1) safety for orbital tissues, (2) uniform diffusion throughout the orbit, (3) adequate contrast with soft tissue, (4) minimal discomfort to the patient. Air, as a contrast medium, has proved most satisfactory for delineating lesions and fulfilling these criteria.[1]

The only other contrast medium which has been investigated to any great extent is iodopyracet (Diodrast). Manchester[2] has found that the injection of 3 to 5 cc. of a 35% solution of iodopyracet "is painful and may produce an alarming amount of tissue necrosis, particularly in the sclera and orbital fat." For these reasons, he does not advocate such injections. When the iodopyracet was preceded with hyaluronidase, he found the procedure to be somewhat safer, but he noted spasm of the central retinal artery in one patient. Other investigators[3] have recently used a 17% solution of iodopyracet and have noted no complications in four patients. The use of other liquid opaque contrast media, such as thorium dioxide (Thorotrast) and iodized oil (Lipiodol), has been discarded because of tissue damage, poor diffusability, and persistence of the contrast material in the tissues.

Twenty-six patients were subjected to retrobulbar air injection, without evidence of damage to orbital structures. The air was completely absorbed in 72 to 96 hours, with restoration of full preinjection mobility of the globe. Neither visual fields nor visual acuity has been altered by the procedure. Diffusion has proved satisfactory, with air visualized in all aspects of the orbit when properly injected. Although air provides less contrast with orbital structures than does

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radiopaque contrast medium, this disadvantage is far outweighed by the safety and diffusability of this medium when combined with planigraphy.

The injection of air under pressure did produce discomfort to the patients. This distress was transient, however, and was not accompanied by the local irritative symptoms reported with many of the opaque contrast media. Sufficient preinjection analgesia with meperidine (Demerol) (75 to 100 mg.) minimized the discomfort produced by the sudden increase in orbital pressure. Although one instance of nonfatal air embolism has been reported in a case of orbital angioma,[1] this complication has not been encountered in our series.

The injection of air into the orbit was performed only after all other diagnostic tools had been employed. Special care was taken to avoid this procedure in any case which clinically might have been an acute infectious process.

Technique—Air Injection and Radiography

Air injection was carried out on patients who had previously received an analgesic such as meperidine. Local anesthesia tried in a few cases at the time of injection did not seem to relieve or avert discomfort and so was discontinued.

The injection was made using a 24-gauge 5 cm., short beveled needle on a 50 cc. Luer-Lok syringe. The needle was introduced just above the inferior orbital margin at the junction of the medial two-thirds and the lateral one-third in all cases. The needle was directed into the posterior aspect of the muscle cone, and aspiration was attempted to assure that the tip was not within a vessel. Twenty to thirty cubic centimeters of air was injected rather rapidly. The needle was then withdrawn approximately half its length and redirected superiorly and slightly medially to enter the muscle cone a short distance behind the globe. After aspiration was attempted again, an additional 5 to 8 cc. of air was injected. Some of the air injected usually escaped into the lids and beneath the conjunctiva, but this did not produce untoward effects. The amount of air injected to outline large masses was of necessity decreased accordingly. Our experience has been that unless the air injection obviously results in increased intraorbital tension and a secondary proptosis the amount of air retained within the orbit is inadequate.

Following the injection of air the x-ray examination may be made leisurely, because the air is slowly absorbed. No particular advantage has been found in attempting to aspirate remaining air after the examination.

The proptosis and subconjunctival air subsided slowly over 72 to 96 hours after injection and resulted in incomplete closure of the eye for the first 12 to 15 hours. A bland ointment applied to the conjunctiva tended to alleviate the side-effects secondary to exposure during this initial period. For this reason and in order to follow the patients more closely during the immediate post-injection period, examination has been performed only on hospitalized subjects.

Good technique in filming proved most important. Since the complete examination required a rather large number of films, with associated radiation exposure to the patient, preliminary scout films were done routinely in order to avoid repeating the entire series for technical reasons. A Picker horizontal-vertical motor-driven planigraph was used which had a focus film distance of 40 in. and a 30-degree sweep, giving an approximately 7 mm. depth of focus. The factors were 50 ma., two and one-half seconds, and a kv. range of 50 to 65.

A brief review of the principles of planigraphy may be of interest to those

not actively engaged in the practice of roentgenography. Because in an ordinary roentgenogram all the structures throughout the thickness of an anatomic part are superimposed and at times confusing, a technique has been devised for making a radiograph of a desired plane in the body. This plane is kept in focus while at the same time structures in front of or behind are blurred out. This is accomplished by maintaining a fixed relationship to one another of the x-ray tube, the plane of the anatomical part desired, and the x-ray film. The x-ray tube and film move in opposite directions during the exposure, with the plane desired acting as a pivot point. Since the "shadow" of a structure in the plane desired always falls on the same area of the film, practically no blurring of that image occurs. However, structures above or below the desired plane (pivot level) do not cast their image on a constant area of the film and are therefore blurred.

In actual practice, the x-ray tube and the Bucky tray beneath the table top, carrying the film, are connected by means of a metal rod. This rod and mechanism for adjusting a pivot point on it to various heights above the table top are behind the x-ray table, so that they do not lie in the beam. The patient is first positioned on the table, and the pivot point is then adjusted at various heights above the table, corresponding to measured levels or planes through the patient. At each level a separate film is exposed while the tube and Bucky tray are in synchronous motion in opposite directions. The result is a series of films, each being in focus at a different level.

Although some authors have recommended sections at 0.5 cm. intervals,* sections 1 cm. apart have proved quite adequate for our studies. After trying various head positions, we found that the most suitable were straight lateral and posteroanterior (PA) views. The forehead was positioned 1 to 1½ in. above the table top, in order to project the petrous ridges below the orbits. In the lateral position the patient was measured so that sections were made in the sagittal plane at 1 cm. intervals from the side to the midline of the skull, a total of four exposures for each orbit. In the PA position, sections began about 0.5 cm. posterior to the cornea, progressing posteriorly to the optic foramen for a total of five sections at 1 cm. intervals.

Results and Radiographic Interpretation

Twenty-five retrobulbar air injections were performed. Of this number, eight were done on normal orbits for purposes of developing the technique and establishing the appearance of the normal air-filled orbit. Seventeen injections were done on patients with exophthalmos. In three patients with a presumptive diagnosis of thyrotropic disease, air injection provided no additional information. One patient was examined twice, the second time as a follow-up. Retrobulbar air injection with planigraphy in 6 of the remaining 13 cases delineated space-occupying lesions which could not be localized by routine x-ray examination. All six were proved by surgical exploration and biopsy. In only one of these, the first examination performed by us, was the location of the tumor misinterpreted. In retrospect, the localization is obvious. An accompanying Table lists results in more detail.

PA planigrams following air injection in a normal orbit demonstrated the globe, in the anterior sections, as a regularly rounded dense image approximately 2 cm. in diameter (Fig. 1*a*). Sections posterior to the globe revealed the optic

* References 1 and 4.

Summary of Retrobular Air Injections on Seventeen Patients with Exophthalmos

Case	Satisfactory Examination	Correct Localization	Pathology Diagnosis	Remarks
1	Yes	No	Pseudotumor	Misinterpreted at time of examination, obvious in retrospect
2	No			Thyrotropic exophthalmos
3	Yes	Yes	Pseudotumor	
4	No			
5	Yes	Yes	Pseudotumor	
6	Yes	No tumor described		Thyrotropic exophthalmos
7	No		Mixed tumor of lacrimal gland	Preoperative diagnosis made clinically and on routine x-ray examination
8	No			
9	Yes	Yes	Leiomyoma	
10	No		Lymphoma of eyelid	
11	Yes	Yes	Overgrowth of bony orbital walls	Confirmed routine x-ray findings
12	Yes	Yes	Pseudotumor	
13	Yes	No tumor described		Thyrotropic exophthalmos
14	Yes	Yes	None from orbit; breast biopsy: carcinoma	Confirmed routine x-ray diagnosis of orbital metastasis
15	Yes	Yes	Foreign body granulomatous reaction	Confirmed routine x-ray findings
16	Yes	Yes		Follow-up examination on previously biopsied pseudotumor
17	Yes	Yes	Pseudotumor	

nerve occupying the appropriate center of the orbit and appearing as a stellar image roughly 1 cm. in diameter (Fig. 1*b*). The loose connective tissue surrounding the optic nerve probably accounts for its large size. Extending outward from the optic nerve (Fig. 1*b*), the four obliquely directed extensions of the extraocular muscles are visualized in hazy outline.

The lateral sections of the normal orbit revealed the outline of a major portion of the globe, the juxtabulbar portion of the optic nerve, and, in many cases, the superior and inferior extraocular muscles (Figs. 2 and 3*a*). Lateral sections near the midline are difficult to interpret because of confusing air

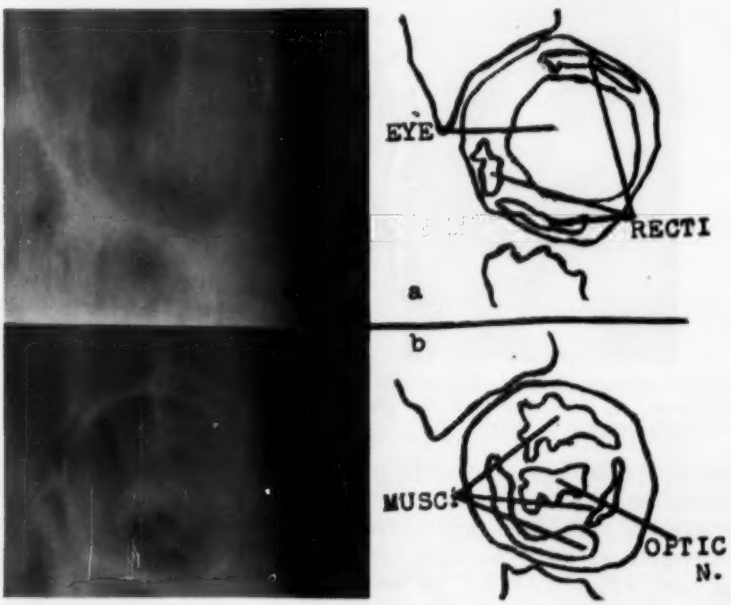

Fig. 1.—Posteroanterior planigrams of normal orbit. (*a*) Through eye, (*b*) posterior to eye.

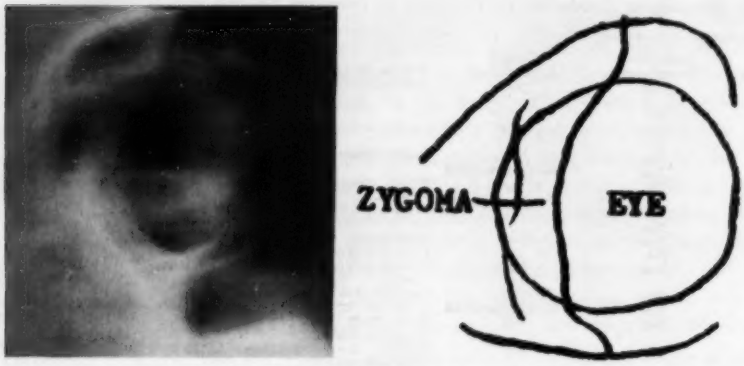

Fig. 2.—Lateral planigram of normal orbit.

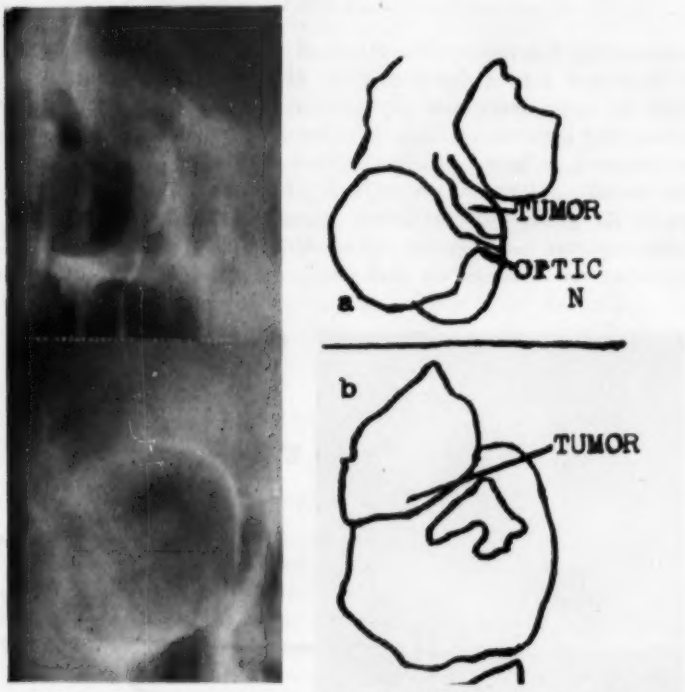

Fig. 3.—White man, aged 58. Foreign body granulomatous reaction of bone extending into orbit. (*a*) Lateral and (*b*) PA planigrams. (Films submitted by U.S. Veterans Administration Hospital, St. Louis.)

shadows in the ethmoid sinuses. In general the PA sections have proved more informative than the lateral ones.

In abnormal orbits the demonstration of pathology depended upon displacement or compression of the globe, optic nerve, or muscles associated with an intraorbital mass (Figs. 3, 4, 9). In some cases the picture was simply one of enlargement of a normal structure without recognizable displacement (Figs. 5, 6, 7, 8). The x-ray examination after air injection indicated the advisability

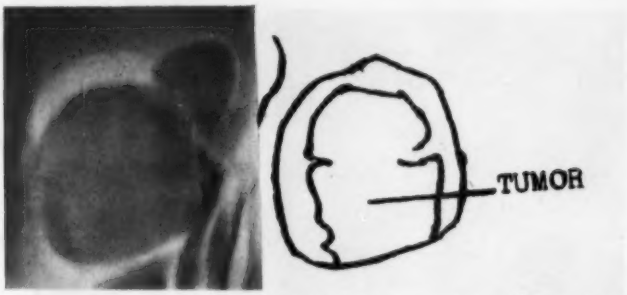

Fig. 4.—White woman, aged 45. Leiomyoma on the floor of the orbit displacing the eye superiorly.

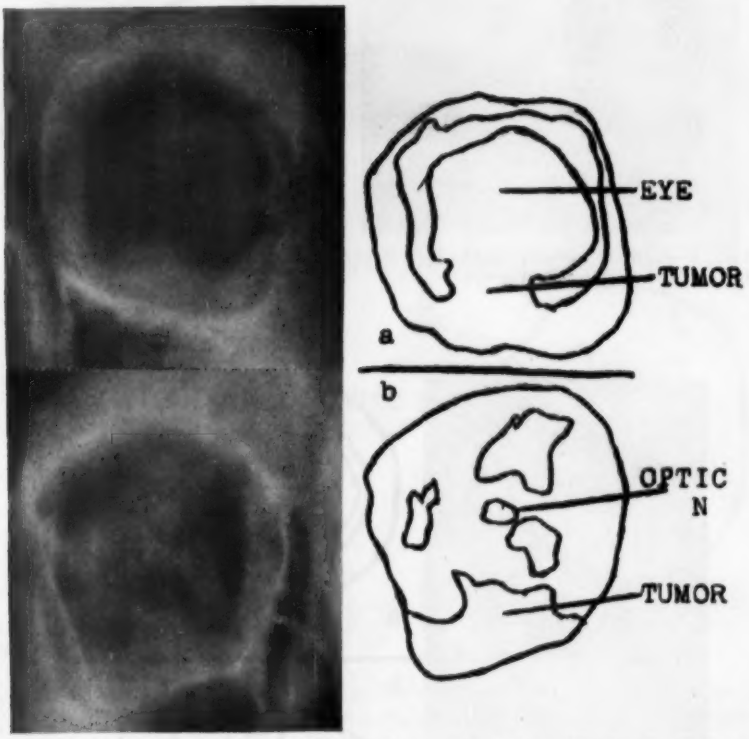

Fig. 5.—White woman, aged 47. Pseudotumor, inferior. Planigrams (*a*) through and (*b*) posterior to the eye.

of a comparatively simple inferior surgical approach in some patients, thus avoiding unnecessary and more complicated superior or temporal exploration.

Bilateral air injections have recently been used. As demonstrated in Figure 9, this procedure permits direct comparison of the normal left side and the inferomedial tumor mass in the involved right orbit.

The absence of air in a part of the orbit did not necessarily mean the presence of a space-occupying lesion. It was not always possible to distribute air uniformly about the orbit, and so diagnosis could not be established solely on the

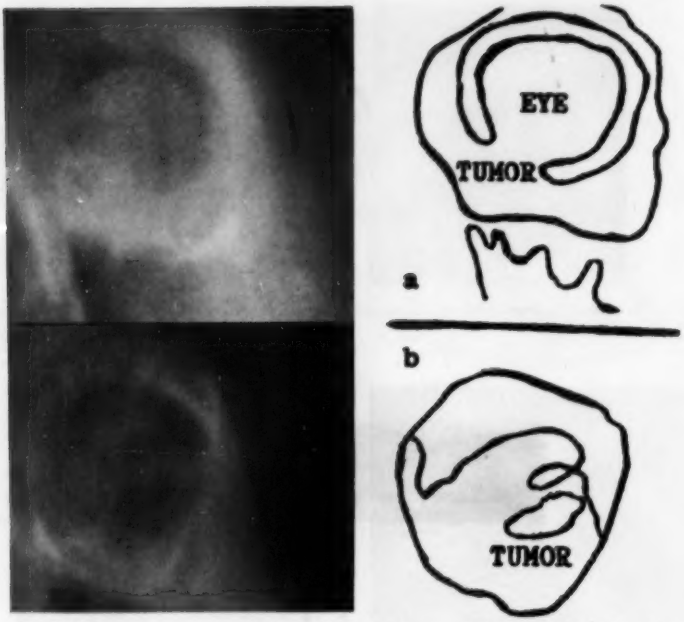

Fig. 6.—White woman, aged 58. Pseudotumor, inferomedial. Planigrams (*a*) through and (*b*) posterior to the eye.

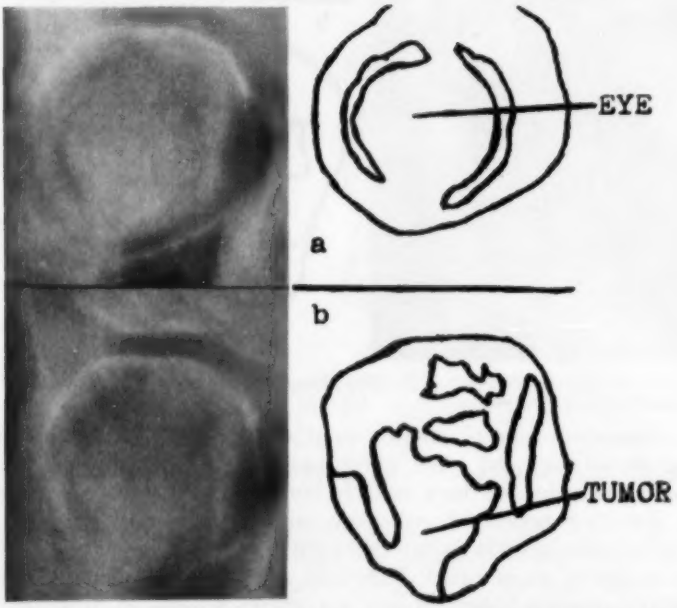

Fig. 7.—White man, aged 58. Pseudotumor, inferior. Planigrams (*a*) through the eye anterior to the tumor and (*b*) through the posterior portion of the eye and the tumor.

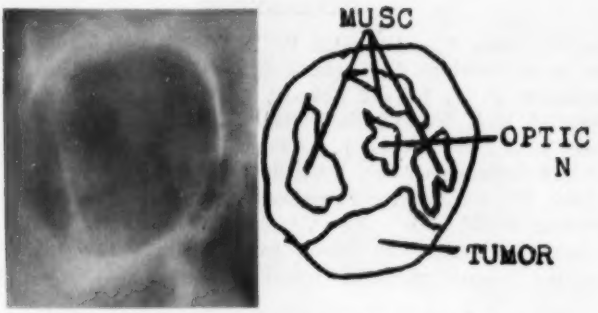

Fig. 8.—White man, aged 59. Pseudotumor, inferior.

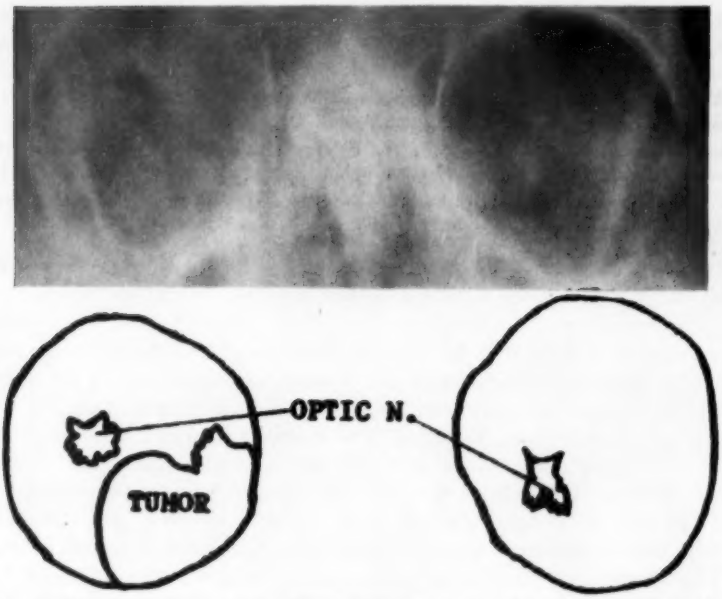

Fig. 9.—Negro man, aged 28. Pseudotumor, inferomedial, with temporal displacement of orbital structures. This is a bilateral air injection, with the pseudotumor in the right orbit.

basis of incomplete filling. This served to emphasize the fact that the interpretation of this examination must involve close collaboration between the radiologist, opthalmologist, and neurosurgeon, with due consideration given to the clinical findings.

Conclusions

1. Retrobulbar air injection with planigraphy delineates some space-occupying lesions transparent to x-ray.

2. The procedure provides evaluation of tumor volume and position.

3. The technique has proved innocuous to orbital tissues and has resulted in minimal discomfort to the patients.

Dr. Hugh M. Wilson and Dr. Bernard Becker gave advice and encouragement in this study. Mr. Joseph Dolan gave technical assistance.

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Fungus Keratitis

A Report of Three Cases

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Since the widespread use of cortisone and antibiotics, an alarming rise in the incidence of fungus infections in various organ systems, such as the respiratory and gastrointestinal tract, has been noted by many observers. The experience reported here suggests that this may be true of the eye as well. From the time of Theodore Leber's [1] first report of aspergillosis of the cornea, in 1879, mycotic keratitis has been the subject of an occasional case report, averaging little more than one case per year in the ophthalmic literature in the subsequent three-quarters of a century. However, in the past year (1955) there appeared in the literature six new case reports of fungus keratitis.

The purpose of this paper is threefold: (1) to report three cases of corneal ulcer in which fungi were demonstrated in the enucleated specimens; (2) to restate the necessity for etiologic diagnosis, both clinical and pathological; (3) to consider the role of cortisone and antibiotics in the pathogenesis of mycotic keratitis.

The recent report by Mitsui and Hanabusa [2] of four cases of fungus keratitis following topical corticosteroid therapy for a miscellancy of other ocular conditions led us to regard with suspicion an eye enucleated for an uncontrolled hypopyon ulcer in which there was a long history of corticosteroid therapy. The pyroxylin (Celloidin) sections of this specimen stained with routine hematoxylin and eosin showed an acute pyogenic inflammatory process in the anterior segment. Further sections, however, stained with periodic acid-Schiff (McMannus [3]) technique, showed a gross infestation with a fungus which was tentatively identified * from its morphological characteristics as one of the aspergilli. Figure 1 shows the marked contrast between the two comparable sections of the cornea as seen under the same magnification.

After this experience, all new specimens received in the ophthalmic pathology laboratory with a clinical diagnosis of any ocular infection were stained with periodic acid-fuchsin as well as with routine hematoxylin and eosin. This demonstrated a second case. Then, review of the specimens received in the recent preceding months revealed a third case of keratomycosis. These three eyes had been enucleated in a period of a little more than a year.

Two of the three following cases were submitted from outside hospitals, and one, from our department.

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From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine. Trainee, National Institute of Neurological Diseases and Blindness (Dr. Ley).

* Morris Moore, Ph.D., mycologist for the Department of Dermatology, Washington University School of Medicine, assisted in this study.

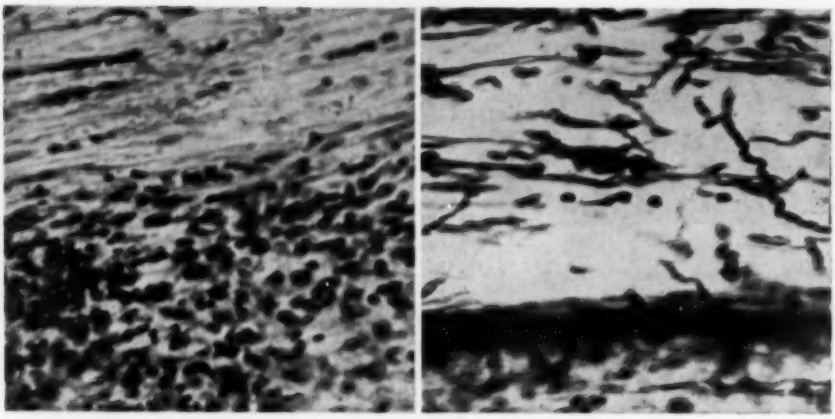

Fig. 1 (Case 2).—On the left is a high magnification of a section of the infected cornea stained with hematoxylin and eosin. On the right is a section of the same cornea under the same magnification stained with periodic acid-Schiff stain.

Report of Cases

CASE 1.—A 61-year-old white farmer was referred to the consulting oculist by his family physician approximately three weeks after he had scratched his left eye while working in a cornfield.

On the first examination the vision was O. D. 20/20, O. S. 20/50. There was marked injection of the left eye and a deep 2 mm. diameter corneal ulcer. There were cells and flare in the aqueous. The patient was hospitalized for treatment with topical application of cortisone, bacitracin, and sulfacetamide to the left eye at frequent intervals. The eye appeared to respond promptly to this therapy, and the patient was discharged with infiltrate resorbing and the eye quiet at the end of a week. Two weeks after discharge from the hospital (five weeks after the injury) the patient returned to the oculist with signs of severe infection. Vision in the left eye had decreased 20/200; pain was intense. The globe was deeply injected, and there was a deep infiltrate 5 mm. in diameter. Despite numerous subconjunctival penicillin injections, systemic cortisone, and pyrexia with typhoid vaccine, the lesion rapidly took on the aspects of a pyogenic serpent ulcer. Because of advancing infection and intractable pain the eye was enucleated on Dec. 6, 1954, eight weeks after the initial injury.

No cultures were obtained. Urinalysis, blood cell counts, blood sugar determinations, and serologic tests were normal.

Pathological Examination.—Hematoxylin-and-eosin-stained sections showed destruction of the anterior two-thirds of the stroma over an area approximately 3 mm. in diameter. The surface in this area was covered with a pyogenic exudate, and the corneal lamellae were invaded by polymorphonuclear leucocytes. The endothelium of the anterior chamber was replaced by inflammatory exudate in which polymorphonuclear leucocytes predominated. The rest of the posterior segment was normal. The periodic acid-Schiff stain showed the exudate on the surface to be made up almost entirely of mycelia, and hyphae were seen infiltrating throughout the cornea and into the anterior chamber (Fig. 2).

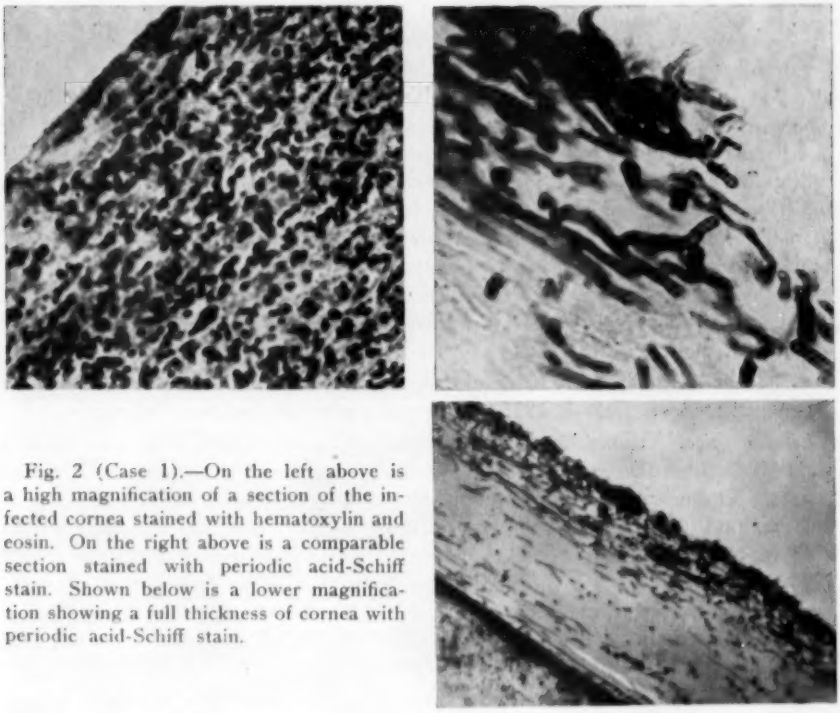

Fig. 2 (Case 1).—On the left above is a high magnification of a section of the infected cornea stained with hematoxylin and eosin. On the right above is a comparable section stained with periodic acid-Schiff stain. Shown below is a lower magnification showing a full thickness of cornea with periodic acid-Schiff stain.

CASE 2.—A 56-year-old farmer was struck in the right eye with a particle of corn from a hammer mill and was given treatment by his local physician on the same day. Because of persisting pain, he was seen five days after the injury by the referring oculist. He noted two small abrasions in the upper central cornea, with infiltration and ciliary spasm but no cells or flare. Treatment was topical oxytetracycline and hydrocortisone drops at frequent intervals during the day and chlortetracycline ointment plus homatropine at bedtime. After one week treatment was changed to neomycin and hydrocortisone drops. Infiltration persisted, and the cornea stained at the end of two weeks.

The patient was not seen again until five weeks later, when he returned with complaint of photophobia, but the eye appeared normal save for a corneal scar.

Right eye was refracted one month later, with corrected vision of 20/20−1. One week after the refraction, an episode of conjunctivitis in the right eye was treated with the same regimen of three successive antibiotics with hydrocortisone. After three weeks of this therapy, there was a keratitis involving the upper third of the cornea. Within 10 days frank hypopyon had developed and the patient was hospitalized for two weeks, during which time he received daily 80 to 120 units of corticotropin intramuscularly in gel form or intravenously plus topical and systemic antibiotics and topical hydrocortisone (except the last four days). X-rays for intraocular foreign body were negative, as was a complete medical examination. Laboratory findings were within normal limits. One blood agar culture grew "Gram-negative bacilli," which were not further indentified.

On admission to McMillan Hospital, the patient was in severe pain. Vision in right eye was questionable hand motion with good light projection in all quadrants. The left eye had 20/20 vision and was normal in all other respects also. The right eye showed chemosis of the lids and beefy red bulbar conjunctiva. The cornea was lusterless and of a dirty gray opaque color with a dense yellowish opacity over the upper two-thirds. The pressure was firm to palpation. No fundus reflex could be obtained. Slit lamp examination showed marked corneal edema, infiltration, and hypopyon. The nasal edge of the well-dilated pupil could be seen, but not the lens or other anterior chamber details. Blood pressure and remainder of physical examination were within normal limits except for 3+ pitting edema of lower extremities. Urinalysis, hemoglobin, red blood cell count, blood sugar, and NPN were within normal limits. White cell count was slightly elevated. Culture on blood agar showed no growth after 48 hours.

The eye became stony hard and the pain was unremitting; hence the eye was enucleated on June 1, 1955, five months after the original injury.

Pathological Examination.—Hematoxylin-and-eosin-stained pyroxylin sections showed deep erosion of the cornea with destruction of the upper half of the stroma. There was dense infiltration of the corneal lamellae with polymorphonuclears and round cells. There was a heavy exudate over the endothelium and obliteration of the angle by cellular debris. The iris stroma was thickened and infiltrated with many polymorphonuclear leucocytes. The lens, vitreous, retina, and optic nerve were unremarkable. Sections stained by periodic acid-Schiff stain showed mycelia spread throughout the layers of the corneal stroma and extending into the exudate in the anterior chamber (Fig. 3).

CASE 3.—A 66-year-old white farmer scratched his right eye with a leaf while pitching feed to his livestock. Four days later the eye became red and painful and was treated by his family physician with yellow mercuric oxide, atropine, and bandages. In spite of these measures the eye became worse.

One week later he was referred to the oculist who submitted the specimen. On this examination the vision was O. D. 20/400, O. S. 20/20. There was a deeply infiltrated ulcer involving more than one-third of the cornea. The patient was hospitalized. The ulcer was cauterized with trichloroacetic acid, and the thermophore was applied. Therapy consisted, in addition to this, of systemic penicillin, a trypsin preparation (Parenzyme), and cow's milk intramuscularly. Chlortetracycline was given topically for the first two days, but it was discontinued because the eye became worse. Five days after admission gross hypopyon developed and the patient was placed on topical oxytetracycline and hydrocortisone for the next three days; then oxytetracycline was given systemically for a week. Thermaphore cauterization was repeated, as was intramuscular cow's milk and trypsin. By the end of the second week a descemetocele developed and four-fifths of the cornea was involved in the ulcer. The eye did not improve after a paracentesis, and it was enucleated on Dec. 16, 1956, one month after the original injury.

No cultures were obtained; blood cell counts, blood sugar, serology and urinalysis were normal.

Pathological Examination.—Hematoxylin-and-eosin-stained cellodin sections showed a large perforated central corneal ulcer with prolapsed uveal tissue. There was edema of the cornea, destruction of Bowman's membrane and the anterior half of the stroma. There was marked infiltration of the corneal lamellae with

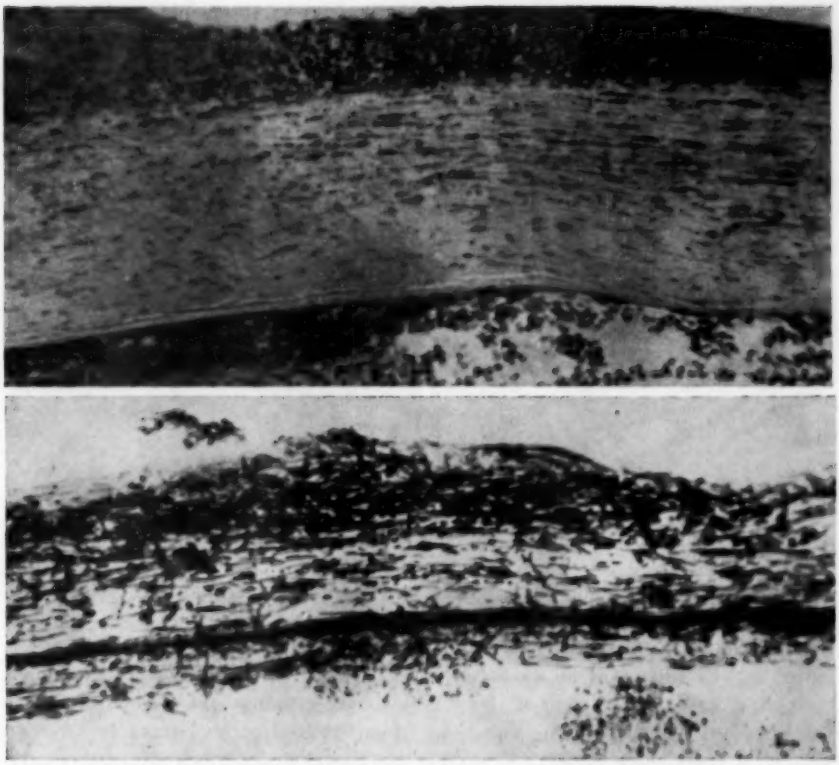

Fig. 3 (Case 2).—At the top is a hematoxylin-and-eosin-stained full thickness of cornea showing surface exudate and destruction of the anterior stroma above and the exudate on Descemet's membrane below. At the bottom is a periodic acid-Schiff-stained full thickness of cornea showing mycelia throughout.

polymorphonuclear cells and fibroblastic proliferation. Descemet's membrane showed reduplication. The iris was adherent to the cornea and was swollen with inflammatory exudate. There was massive subchoroidal hemorrhage. Periodic acid-Schiff-stained sections showed mycelia in the deep corneal stroma with hyphae penetrating through Descemet's membrane (Fig. 4).

Comment

The preceding cases have several features in common. All three patients were farmers, which occupational coincidence has been noted by many previous authors. All had sustained trivial corneal injuries with vegetable matter. All were treated for varying periods with corticosteroids and antibiotics. In none had the diagnosis of mycotic infection been made prior to enucleation nor, for that matter, prior to the use of special staining technique.

It must be stated here that, when the hematoxylin-and-eosin-stained sections were minutely examined in retrospect, a few ghosts of mycelia could be seen on an occasional section; nevertheless, the vast bulk of the organisms remained hidden in the hematoxylin-and-eosin preparations and thus were overlooked on routine examination. As long ago as 1913, Verhoeff [4] demonstrated unequivocally the value of differential stains in demonstrating the causative organism in an ocular disease, and this point need not be labored further.

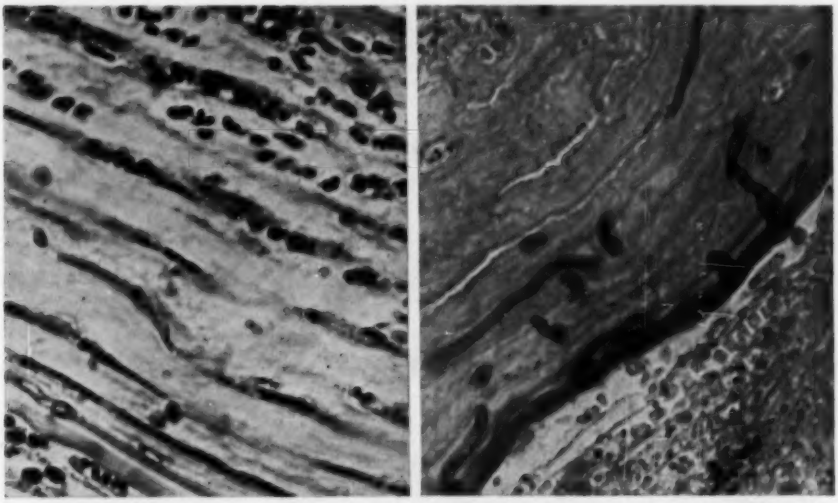

Fig. 4 (Case 3).—On the left is a high magnification of a section of cornea stained with hematoxylin and eosin, and on the right is a comparable section stained with periodic acid-Schiff stain.

Hervouet and Lenoin,[5] in reporting two cases of aspergillosis of the cornea, pointed out that this fungus keratitis presents most frequently as a common hypopyon ulcer and usually is not recognized as a fungus infection. This observation was based in part on the solid ground of their own oversight; for although their first case was diagnosed by smears and scrapings the second one was not discovered until pathologic sections of an excised corneal transplant button were examined in retrospect. Certainly the above-cited experience further confirms the impression that the pathologist as well as the clinician must be on guard constantly for fungi in every case of hypopyon ulcer.

The presence of gross mycelia in the surface exudates in two of these specimens (Figs. 2 and 3) indicates that a smear and a culture of the organisms could easily be obtained from a scraping of such ulcers.

The role of fungi in these cases is difficult to assess, there being three possibilities. The first is that the fungus may be the primary pathogen or essential etiologic agent; the second is that it may act as a secondary invader in a bacterial or viral infection, altering the course of the disease, and the third is that the fungus may be present only as a saprophyte. Although in these three cases the original role of the fungus cannot now be ascertained, nonetheless the massive invasion of cornea and extension of the hyphae into the anterior chamber suggests an active role of the fungus in the end-stage of the disease process that was seen in the pathology laboratory.

In the first paper on keratomycosis Leber[1] considered the question of symbiosis. He made simultaneous inoculations of the Aspergillus isolated from his patient and micrococci on sterilized corneal tissue and demonstrated that both of these organisms could coexist on the same medium. However, when he inoculated a pure culture of this same Aspergillus into a rabbit's cornea, a violently destructive lesion occurred within 24 hours. Another illustration of symbiosis was provided by Pautler and co-workers.[6] In this instance clinical history (including use of topical cortisone) very closely paralleled that of two

of the cases reported here. These authors noted the consistent presence of Micrococcus pyogenes var. aureus in all of the cultures as well as Monosporium apiospermum. They were able to demonstrate the presence of Gram-positive cocci as well as the fungus in their paraffin sections. S. Fazakas [7] reported that he was able to demonstrate symbiosis as well as antibiosis to the same bacterium using a culture of the same fungus of different ages. In a later report [8] he states in keratomycoses secondary to bacterial infection there was a cessation of bacterial

Summary of Reports of Corneal Disease Incident to Topical Corticosteroids

Observer	Fungus Keratitis	Acute Pyogenic & Disciform Keratitis	Dendritic Keratitis	Initial Conditions
Mitsui[2]	4	1		Blepharitis & conjunctivitis (8 cases)
Moser[13]		6		Dendritic keratitis (12 cases)
				Fuchs' dystrophy (3 cases)
Hogan[11]	1	6	6	Serous iritis*
				Interstitial keratitis*
				Postoperative iridectomy*
				Phlyctenular keratitis*
				Corneal infiltrate*
Braley†		2		
Offret[14]		2		

* One case each.
† Braley mentions these two cases in discussing the paper by Hogan.[11]

growth upon the advent of the mycosis. A. Fazakas [9] has observed the largest single series of keratomycoses (a total of 34 cases since 1931). Twenty of his cases were primary keratomycoses, and fourteen were secondary to other ocular infections. He has been able to demonstrate primary pathogenicity of certain species and strains of fungi by inoculating experimental animals with cultures of fungi obtained from human lesions and reisolating that same fungus from the experimental lesion.

The essential problem posed by the three cases reported here is whether the use of antibiotics and corticosteroids altered the clinical course in such a way as to allow the lesion to become seriously infected by the fungus.

In the first place, it is possible that the growth of the fungus itself can be modified by therapy. In their report of four cases of fungus keratitis, Mitsui and Hanabusa [2] showed that corticosteroids favor the growth of fungi. In a series of 63 cases of various ocular diseases treated at least three weeks or more with topical cortisone, there was a 49% increase in the incidence of fungi isolated from conjunctival cultures.

Secondly, it is possible that normally saprophytic or symbiotic fungi may become facultative pathogens by alteration in host resistance produced by corticosteroid therapy. The development of a fungus infection of the cornea in a patient receiving topical corticosteroid therapy for another ocular disease was first mentioned by Thygeson and co-workers.[10] Certainly, the most convincing evidence is the four proved cases reported by Mitsui and Hanabusa,[2] which were mentioned previously. Besides fungus keratitis, there have also been reports of other acute pyogenic ulcers, dendritic keratitis, and disciform keratitis appearing as complications of topical corticosteroid therapy. These cases are summarized in the Table.

Furthermore, preliminary animal experiments which are to be published by one of us (A. P. L.) demonstrated that either topical corticosteroids or certain antibiotics may facilitate some corneal fungus infections.

Although much experimental work is needed concerning the effect of corticosteroids and antibiotics on fungus lesions of the cornea, the summation of the clinical experience to date indicates that the application of corticosteroids to corneal lesions is made at the risk of facilitating mycotic, bacterial, or viral infections. Corticosteroid and antibiotic therapy would seem to be particularly hazardous for a cornea with an epithelial defect or in the presence of any active infection.

Summary and Conclusions

Three cases are reported of eyes enucleated for hypopyon ulcers in which fungi were demonstrated by selective staining of pathological sections. These three cases accounted for all of the specimens received in this laboratory in a period of a little more than one year that were enucleated with the diagnosis of primary pyogenic ulcer.

The importance of etiologic diagnosis by scraping and culture is emphasized.

The potential hazards of cortisone and antibiotic therapy in facilitating fungus keratitis are emphasized.

The following ophthalmologists referred the cases to us: Dr. M. K. Hirschfelder, Centralia, Ill. (Case 1); Dr. J. E. Helm, Olney, Ill. (Case 2); Dr. W. H. Garnier, Stillwater, Okla. (Case 3).

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Pitfalls in Strabismus Surgery

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Although ocular muscle surgery is usually considered to be a minor procedure, serious complications may occur, some of which may result in the loss of the eye. Most of them fortunately, do not jeopardize the eye but cause an unfavorable or unsatisfactory surgical result which could have been avoided.

The following presentation is a review of some of the causes of unsatisfactory results in the surgical management of strabismus cases. Such a review emphasizes the need for the utmost exactness in the management of these cases. Strict attention to detail can make the difference between mediocre and good results.

The subject will be considered from the following standpoints: A. general considerations, B. factors applying to all the muscles, C. factors applying to the individual muscle.

A. General Considerations

1. In considering the various pitfalls in ocular muscle surgery, we should first consider the physician himself.

It is important for him to be up to par physically and mentally in order to do his best work. If he has had improper rest the night before surgery or if he is overtired owing to too much work, or if he is ill for any reason, such as an acute respiratory infection, his efficiency is lowered and surgical complications are likely to occur. There are times when the physician needs the sedative rather than the patient.

2. Complications arise when the patient is not up to normal physical standards.

In children, respiratory infections are common. Even if the temperature is normal, the physical state of the patient may not be equal to the shock of ether anesthesia. A lowered vitality or such physical states as thymus enlargement, diabetes, etc., should be carefully considered before surgery is carried out. In the older patients, it is particularly important that they be in as good physical condition as possible. Physical ailments such as respiratory infections and systemic diseases may contraindicate surgery.

3. It is hazardous to combine another operation with muscle therapy.

There is a tendency sometimes to combine the muscle operation with a tonsilectomy or circumcision in order to save an extra trip to the hospital. Doing two operations simultaneously not only disturbs the eye surgeon but prolongs the anesthesia unduly, which may produce complications such as pneumonia. Once in my experience this resulted in death from a respiratory complication.

4. Do not operate too soon after a conjunctival inflammation.

Although the acute phase may have passed, a low-grade infection of the conjunctiva may remain and an operation may cause an acute exacerbation of the infection. Surgery of the eye muscles necessitates working deep in the orbit, and every precaution against infection should be taken. An infection in the deep tissues will produce excessive adhesions and lessen the effectiveness of the surgery.

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5. Do not operate in the presence of an infected lacrimal sac.

Frequently low-grade lacrimal infection is present and overlooked, especially in the very young. In such cases the operative field is exposed to an infection which may involve the deep tissues and result in excessive scar formation.

6. Do not operate too soon after an injury to an eye muscle.

It has been my experience that one should wait several months before the final outcome can be predicted; in the average case, most of the healing has taken place in six months. However, one may delay too long, in which case secondary changes in normal muscles may occur.

7. There is some hazard in giving anesthesia to a very young child.

There is a risk in operating on very young children, although the risk may be justified in certain instances. If a good anesthetist is available, and if the muscle defect is marked and is obviously a developmental anomaly, an operation is justified on a young child.

8. It is important to prepare the patient properly for anesthesia.

He should abstain from fluids and food the morning of the operation and have the proper hypodermic medication, with sufficient time allowed for the medication to take effect before the anesthesia is started.

9. It is important that strict sterility be maintained.

Every precaution should be taken in sterilizing the instruments, gloves, gown, and operative field. As mentioned before, not only does infection prolong the healing but excessive scar tissue is invariably formed, which lessens the effectiveness of the surgery.

10. Check irrigating and other solutions before preparing the field for surgery.

Mistakes have been made in putting tinctures or strong caustics in the irrigating bottle. In one instance a bilateral corneal leucoma developed, resulting in blindness.

11. Foreign matter such as cotton shreds or lashes buried in the operative field creates considerable reaction of the tissues and results in excessive scar formation and adhesions. Cysts may develop in the region of the sutures. Most of these spontaneously disappear, although some must be incised.

12. The patient should wear an identification bracelet.

There should be no question that you are operating on your own patient. Confusion of young patients has occurred, with disastrous results.

13. Keep a record of the surgery necessary.

Before beginning the operation, check your record and refresh your memory as to which muscles are to be operated on and the amount of surgery necessary. In addition, it pays to double check by briefly examining the patient's eyes before the anesthesia is started. This is especially true if you are doing several cases. It may be disastrous to operate on the wrong eye.

14. Poor postoperative care may lead to failures in muscle surgery.

The postoperative care which the patient receives is as important as the operation itself. Such care actually begins on the operating table when the bandage is applied. The bandaging of both eyes is necessary, even though only one may have been subjected to a surgical procedure. The only operation which need not be followed by a bandaging of both eyes is recession of the inferior oblique. The bandage should be held snugly in place with a pressure bandage such as Elastoplast. The first dressing is done on the first postoperative day. The eyes are usually kept bandaged for four or five days, with the exception of the very young child, who has one eye uncovered in 24 hours and arm cuffs applied if necessary.

It is important to restrict the activity of the patient after surgery. As a rule, he should remain in bed for two days, following which he is up but not active. At the end of four or five days peepholes are given during the day and the eyes are again covered at night to prevent injury or early morning use. The peepholes are made by applying adhesive to the glasses. The patient is usually restricted in the use of his eyes for at least two or three weeks, depending upon the type of muscle surgery.

An occasional patient will be encountered whose postoperative reaction is out of proportion to what is usually found. The edema is allergic in nature, and it is apparently a reaction to the suture material. Such a reaction must always be differentiated from an early orbital infection following surgery.

A few weeks after surgery it may be necessary to change the glasses to correct the accommodation-convergence ratio. If visual acuity begins to fall postoperatively, having been improved with occlusion preoperatively, it may be necessary to resort to occlusion again. Postoperative orthoptics is desirable in certain cases.

15. A functional result may be lost because of inadequate treatment.

If evidence indicates that a functional result is possible, a cosmetic result should be classed as a failure. Fusion should be the goal in the treatment of all tropia cases if there is any possibility of obtaining it. Without fusion the patient may develop some other tropia in future years. Orthoptic training may make the difference between success and failure.

16. Do not fail to explain the operative objective to the patient or parents.

They should understand the need for more than one operation in certain cases. This understanding insures better appreciation and cooperation.

17. Do not criticize a previous surgeon's work to the patient or the parents.

This criticism may be prefectly justified, but it not only places the other doctor but makes you less respected by the parents or patient.

B. Factors Applying to All the Muscles

1. Do not operate on a dissociate type of defect.

Surgery on such a case of neurogenic nature will be a failure, because it will not correct the defect and instead transfers it to another field. Such defects are due to lack of central control of the innervational impulses. If, however, it is associated with a mechanical defect, the mechanical defect can be corrected, although the dissociated phase of the problem will still persist.

2. Do not operate when there is a possibility of permanent diplopia.

In apprehensive or neurotic patienets, especially those who have been warned of the possibility of diplopia if they are operated on, there is danger of creating permanent diplopia. This is especially possible in adults who have fairly good vision in both eyes. Although I have performed surgery on such cases without this complication occurring, an occasional patient was conscious of the postoperative diplopia, which persisted in spite of all efforts to overcome it.

3. Do not operate on an eye which had a perforating injury years previously and which shows evidence of a quiescent iridocyclitis.

These more or less sightless eyes may deviate outward or inward. Although in certain instances surgery is justified for cosmetic reasons, it is possible that operating may cause a flare-up of a previously quiescent uveitis which will necessitate enucleation.

4. Improper placing of sutures in the sclera may lead to complications.

It is important to secure a good bite in the sclera when inserting sutures. If the bite is too superficial, there is danger of the suture pulling out. In case it does pull loose from the globe after an operation, the incision should be reopened immediately and the muscle located and resutured in place. Do not place the suture too deep in the sclera. Such an occurrence may cause a weakening of the sclera and inflammation or irritation of the inner coats of the eye. There is a definite hazard in perforating the globe with the needle when inserting the sutures. Such a situation may cause endophthalmitis to develop.

5. Abnormal retinal correspondence can lead to failure in tropia surgery.

Abnormal correspondence when untreated prior to surgery will usually develop at some new abnormal angle postoperatively. It is possible that the abnormal correspondence may disappear if an exact correction is obtained. Fusion is never developed unless abnormal correspondence is eliminated.

6. Do not delay surgery when it is indicated.

It is a mistake to delay surgery on patients with tropia to observe them further when there is obviously a mechanical problem. If surgery is indicated, it must be done early. In pronounced cases where a mechanical factor is at the basis of the problem, I operate as early as 9 months of age, provided a good anesthetist is available. The earlier the defect is corrected the more satisfactory is the outcome.

7. Do not operate without careful study of the muscle problem.

When a case is of long standing and several muscles seem to be involved, owing to secondary changes, a complicated diagnostic problem is present and it is only through repeated examination can the best results be obtained. Repeated study leads to more accurate diagnosis and is advisable even in the less complicated cases.

8. Failure to recognize a "nervous" factor may cause poor results.

The apprehensive patient with esotropia presents a problem which is difficult to evaluate and requires careful study. The busy physician who sees a patient on only one or two occasions is likely to misjudge the amount of deviation actually present. A child will have far more esotropia in the presence of strangers than when playing quietly at home. The deviation to be corrected surgically is that found when the patient is relaxed and at ease.

9. Incorrect diagnosis of the offending muscle or muscles usually leads to an operative failure.

Owing to improper diagnosis, the wrong muscle may be operated on. This complicates the picture by adding another defect to the original defect. The problem is made worse and incapacitates the patient to a greater degree.

10. Failure to recognize the mechanical component of a deviation leads to an unfavorable result.

Valuable time is lost when a mechanical defect is overlooked or ignored and the patient is treated on an innervational basis. Such a situation invariably leads to an unsatisfactory result.

It is often possible to evaluate a mechanical component on the operating table before starting to operate. The effect of general anesthesia upon the position of the eyes of the patient with esotropia varies, depending upon the relative amount of the mechanical and innervational components. The general anesthesia must be deep before the observation of the position of the eyes is of value; under light general anesthesia the eyes may converge excessively. If a tropia

is mechanical, little change in the position of the eyes under deep general anesthesia will be noticed. If it is an innervational esotropia, the deviation disappears entirely and the eyes will assume the parallel position or at times diverge. An esotropia that disappears completely under deep general anesthesia should warn the surgeon of the danger of overcorrection. The same operation will result in more correction if the deviation is largely innervational rather than largely mechanical.

Simple inspection of the position of the eyes prior to beginning the operation requires a few seconds and will often pay dividends. The forced duction test is a valuable aid in determining the amount of mechanical defect present.

11. Another reason for failures in tropia surgery is the failure to recognize an accommodative factor.

The case should be refracted under atropine and a glass prescribed if needed. The glass should be worn for a period of two or three months to allow for the establishment of a new accommodation-convergence ratio. By so doing, the correct evaluation of the accommodative factor in a tropia case prior to surgery is possible. The surgeon who performs either a manifest or a homatropine refraction instead of using atropine in a young patient with tropia is purposely not obtaining the full information, which is usually of great value.

12. The value of a knowledge of the near point of convergence prior to any surgery for strabismus cannot be overemphasized.

One should never perform a bilateral recession of the medial rectus muscles when the near point of convergence is remote (farther than 40 to 50 mm. from the bridge of the average nose). The near point should also be considered in selecting the procedure in exotropia.

13. Failure to recognize the presence of a vertical component leads to poor surgical results. In the presence of a vertical component the results of surgery in horizontal tropias are both variable and unpredictable. A vertical deviation is frequently a mechanical obstruction to binocularity. Vertical components are usually easily identified by a careful study of versions in the six cardinal directions.

The surgeon not only should identify a vertical component in a horizontal deviation but must evaluate it properly. He should determine whether the horizontal or the vertical component should be attacked first surgically. As a general rule, if the vertical deviation is less than one-half of the horizontal deviation, attack the horizontal deviation first. If the vertical deviation is equal to or greater than one-half of the horizontal deviation, attack the vertical deviation first. It is seldom a wise procedure to attack both vertically and horizontally acting muscles in the same operation.

14. A case may show an overcorrection following surgery.

In these cases an esotropia is converted into an exotropia, or a hypertropia is changed into a hypotropia. Overcorrection is usually the result of excessive scar tissue, a muscle pulled loose from its insertion, or poor judgment upon the part of the surgeon in performing more surgery than was needed. To correct an overcorrection requires more surgery than did the original deviation. Merely returning a muscle to its original site is never sufficient to abolish an overcorrection. A good result following surgery on a patient with esotropia which becomes an esotropia again within two or three months postoperatively usually means adhesions.

15. It is difficult to estimate exactly how much surgery to do in strabismus, and it is much more desirable to undercorrect with surgery than to overcorrect.

Correction in two or three steps is indicated in complicated cases of long standing, particularly in dealing with the vertical muscles.

16. Do not do too much on one muscle.

Excessive recession or resection causes a crippling effect and limits the rotation of the globe and may nullify the operative effect. It is better to divide the correction between two muscles. For example, it is better to recess both medial recti moderately than to try to accomplish everything in one large recession to get the desired effect.

17. Do not operate on cases for slight defects if they are cosmetically satisfactory and the possibility of binocularity is nil, such as is found in eyes with defective vision due to an old chorioditis. The case may be made worse.

18. Do not traumatize the tissues needlessly, as trauma increases the scar tissue formation and adhesions.

Reducing trauma to the tissue to a minimum will do much to prevent such an occurrence. Blood clots create adhesions, and it is important that all bleeding be stopped and blood clots removed before the wound is closed. The fascial expansions of the muscle should be cut and not forcefully torn; removing the facial covering of the muscle accentuates scar formation; crushing the muscles with a forceps increases the reaction, and hematoma of the muscles creates a marked reaction.

The insertion of a small piece of absorbable gelatin film (Gelfilm, Upjohn) between the operated on muscle and the adjacent tissues will reduce adhesion formation. It is especially helpful in cases of operation or in operations involving the vertical muscles. Absorbable gelatin film is nonirritating and will not be absorbed for several months. By its presence the cut edges are not in apposition, thus preventing the scar from reforming. I had occasion to reoperate on an area where absorbable gelatin film had been placed six months previously. I found it intact.

19. The wrong surgical procedure produces failures in tropia surgery.

The site of attack may be wrong. For example, if a superior oblique is paretic, recession of the inferior rectus of the opposite eye is a poor choice of operation; strengthening the superior oblique and, in some cases, a weakening operation of the inferior oblique on the same eye are usually much better.

The wrong type of operation leads to poor surgical results. Such operations as a recession or an advancement of the inferior oblique and weakening or shortening operations on the superior oblique are procedures which call for definite indication, and the wrong type of operation leads to trouble.

The same procedure should not be used on every case. To perform a recess-resect procedure in every case of eostropia is poor judgment. It is the operation of choice in many cases of esotropia, but in many others it is a very poor choice.

20. A conjunctival incision should not be made too long or too close to the limbus.

If the surgical incision for any operative procedure on the medial rectus is made at the edge of the plica semilunaris, or as lateral as possible in the case of the lateral rectus, the resultant scar will be less visible. This cosmetic point is of greater interest to the patient than to the surgeon, but it should be considered.

21. It is important to remember that adult confunction tears easily and a retraction suture placed at the limbus will usually pull out, leaving a tear in the conjunctiva. Greater care is necessary in closing such wounds because of the friable state of the conjunctiva.

22. The fascial expansions of the muscles being operated on should be severed.

Some surgeons recess only the primary insertion of a muscle. When only this is done, the operative result may be greatly lessened. If the maximum effect is to be gained from the operation, the primary insertion must be recessed and the secondary insertions must be sectioned. The secondary insertions are of mechanical importance and sometimes are more important than the primary one. The secondary insertions include the check ligaments, the intermuscular membrane, and any of the insertional anomalies. This is especially important in recession of the inferior oblique, where failure to sever the posterior expansion may nullify the result. Lack of consideration of the secondary insertions is the explanation of the wide variation in effect of the operation in different cases.

23. Suppression amblyopia should be abolished preoperatively if possible.

One of the great failures in dealing with strabismus is failure to eliminate amblyopia. Frequently the cosmetic result in the young child is good and we assume that the vision is good. It is not until later that we find the visual defect, too late to develop vision. The opportunity of early childhood when amblyopia can be overcome is missed, and the patient goes through life with defective sight which could have been prevented. To operate upon a child with amblyopia which has not been treated is not advisable. An apparently successful surgical result in the case of esotropia with amblyopia in one eye may change into an exotropia after a time.

Most amblyopia patients where normal anatomy exists will respond to treatment to some degree. Occlusion may be kept up constantly for several months at a time and repeated when necessary. Partial or intermittent occlusion is to be condemned in preference to total and constant occlusion in amblyopia.

24. Failure to give orthoptics reduces the chances for success in certain tropia cases.

Although in a high per cent of the cases a functional result can be attained without orthoptics, it can be attained in a larger percent with orthoptics. It is obvious that if good orthoptics is available the surgeon can increase his chances for success.

An orthoptic technician is invaluable. With her assistance, a great deal of time is saved for the physician in determining not only the position of the eyes but the binocular efficiency. She is also a great help in following the progress of the case after surgery. Orthoptists should not make recommendations concerning surgery. They have neither the background nor the training to do so.

C. Factors Applying to the Individual Muscles

Lateral Rectus

1. In exposing the muscle, make a conjunctival incision well back from the limbus. The scar will not be as conspicuous. The incision should not be longer than necessary.

2. Pull up the conjunctiva when making the initial incision, because there is danger of including the muscle tendon in the incision.

3. Do not strip the fascial sheath off the muscle.

4. As the inferior oblique is frequently attached to the lower margin of the lateral rectus, care should be taken not to sever this muscle or include it in the operative procedures on the lateral rectus.

5. Do not remove too much muscle or recess it too far, as it limits the rotation of the eyeball.

6. Reattach the muscle in the correct alignment.

7. The sclera is very thin beneath the lateral rectus insertion and is easily perforated.

Medial Rectus

1. Do not make the incision any longer than necessary, and place it medially as far as possible (near the plica).

2. Sever the fascial expansions, but do not disturb the fascial sheath of the muscle.

3. Excessive dissection may cause excessive scar formation and adhesions.

Vertical Recti

1. Surgery of the vertical recti (and obliques) is less predictable with respect to result than is surgery of the horizontal recti for the following reasons:

(*a*) Accurate diagnosis is more difficult in patients having involvement of one or more vertical recti.

(*b*) A small amount of surgery on a vertical muscle is more effective than the same amount in a horizontal muscle, and it is difficult to regulate the surgery to such a narrow margin.

(*c*) The variable actions of the vertical recti make exact correction more difficult.

(*d*) The vertical muscles have a very narrow margin of adjustability as compared with the horizontal recti. A deviation may be compensated for in the horizontal field because of the adaptability of the horizontal component, whereas the vertical recti are very stable in their position and have a very limited range of adaptability. Any deviation remaining following surgery is not compensated for to any degree.

2. Avoid excessive recession or resection of a vertical rectus muscle. More than a 4 mm. resection may cause ptosis. Recessing more than 4 mm. may impinge upon the tendon of the superior oblique and cause it to be bound down by scar tissue.

3. Absorbable gelatin film is especially valuable when operating on the vertical muscles, to prevent adhesions.

Superior Oblique

1. The tendon is difficult to find if the technique is incorrect.

2. One may err in severing the fascial sheath instead of the tendon in doing a tenotomy.

3. In doing a tenotomy, do not strip the sheath off the tendon but make a small opening in it, cutting only the tendon. The tendon should be cut adjacent to the medial rectus, as a paralysis may result if the tendon is cut closer to the trochlea.

4. Tenotomy calls for definite indications, and if the operation is not indicated the patient may be visually crippled because of the resulting torsion.

5. Tucking the muscle should be done by approaching from the lateral side of the superior rectus, and only the tendon near the insertion should be tucked. Do not tuck more than 8 mm. of the tendon.

Inferior Oblique

1. Operation at the origin gives unpredictable results.

2. Myectomy or myotomy is not predictable and cannot be undone.

3. More predictable results are obtained in the recession at the insertion. The

recession operation has the advantage that, if too much effect is obtained, the muscle can be reoperated on.

4. It is important to cut the posterior fascial sheath expansion of the inferior oblique in doing a recession. If this is not done, the result may be unsatisfactory.

5. Do not do more than an 8 mm. recession, and keep it in the correct line of pull.

6. The lateral rectus should not be severed in working on the inferior oblique.

7. Care should be taken in working at the insertion because of the danger of injury to the vessels and nerves in the area. The macula is adjacent to the posterior tip of the muscle insertion.

8. Limit the trauma to a minimum, because adhesions result and destroy the result.

9. Absorbable gelatin film placed between the inferior oblique operated on and the lateral rectus will help prevent adhesions.

Medical Arts Bldg. (2).

Causes of Failure in Retinal Detachment Surgery

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A truly statistical determination of the causes for operative failure in cases of retinal detachment in a very difficult task. For one reason, among many, a single series infrequently contains a sufficient number of cases that have been followed closely by the same examiners long enough to determine the eventual fortune (or misfortune) of the eye operated on. Many of us feel that if the retina is well in place four or five months postoperatively the procedure was successful, but most of us have seen an occasional patient who has suffered a recurrence up to a year or more postoperatively, and we may then secretly feel that in truth we did not "cure" this patient but instead neglected to provide adequate operative insurance for that eye's future.

It is also rare that a series of patients with retinal detachment is not "selective" in one form or another. As an example, there are many patients who present themselves for the first time with a detachment of a least six or more months' duration, and their chances of a cure are far less than those of the patient fortunate enough to have been made aware of his condition within a few days or weeks of its onset. As another example, an increasingly large number of patients with retinal detachment being seen by physicians especially interested in the problem are those who have been unsuccessfully operated upon previously; these patients now present themselves for further treatment, their initial problem having been compounded by inadequate care. In neither of these two groups is the physician in the favorable position of knowing the appearance of the fundus picture in the early days of the detachment, and frequently cataractous and secondary retinal changes have made examination of the retina and vitreous considerably less satisfactory than one would desire.

There are also those patients with a retinal detachment who are either unwilling or unable to undergo more than one operative procedure; as will be briefly pointed out later, an unflagging desire in the physician to obtain a cure will lead to repeated operations on these persons, and will materially increase the number of eyes salvaged. It is probably perfectly in order to pose the question, "Why wasn't the patient cured initially?" If the patient is never cured, by one or by multiple operations, the answer to this question will most often go begging. If, however, the patient does respond to further surgery, the operator is in a better position to answer the question with some amount of assurance, if not with a greater degree of equanimity.

Any consecutive number of retinal detachment cases will also include a variety

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of kinds: The so-called "simple" type of detachment, those due to oral disinsertions, those that are true cysts of the retina (giant cysts), those shortly following an otherwise uneventful cataract extraction, and those due to perforating injuries are all examples. One can evaluate fairly well the variable prognosis of each form, and, depending upon the preponderance of one group or another, the operative results will fluctuate.

In reviewing the cases of retinal detachment referred to in this paper we have used only private patients operated upon by us between July, 1951, and July, 1955; we have taken the liberty of excluding retinal detachments due to penetrating intraocular foreign bodies, those detachments due to oral disinsertion, and those patients in whom we felt there was a giant cyst of the retina. We feel that these three types of retinal detachment should not be considered as belonging in the category of "simple" detachment. We have included all other retinal detachments, regardless of the probable length of the disease (from a few days to over six months); aphakic detachments shortly following cataract surgery as well as those developing many months after surgery, and patients with myopia up to and over −20.00 D. Children as well as adults are similarly included.

TABLE 1.—*Cases Cured Compared with Total Number*

	Total Cases, No.	Cases Cured	
		No.	%
Primary cases*	369	300	81.3
Secondary cases†	71	32	45.1
Total	440	332	75.5

* Patients not operated on previously.
† Patients operated on unsuccessfully elsewhere.

A glance at Table 1 will show that a total of 440 cases is considered; of those patients who had not undergone previous retinal detachment surgery, we were able to obtain cures in 81.3%, while our success in those patients who had previously been treated elsewhere was markedly less (45.5%). All in all, we were able to cure 75.5% of the 440 patients.

These figures compare well with those of other recent writers. Hughes [1] reported an over-all cure rate of 67% by diathermy surgery in 375 consecutive cases contributed by members of a symposium. Kennedy and Kazdan [2] reported successful results in 47% of 103 unselected cases. Koenig and Addington [3] achieved 78% cures in a series of 129 cases. In reporting 109 cases, Safar and Vit [4] were able to reexamine 85 of the cases at least six months postoperatively, and 75.3% proved to be "definitely cured." Using surface diathermy, puncture, and injection of air, Rosengren [5] reported 78% cures in 300 cases. Fanta [6] operated upon 204 eyes over a two-year period and obtained 65.4% cures. Weve,[7] who excluded cases that were operated upon previously elsewhere, cured 80% of almost 1000 cases. In reporting 210 detachment operations, Neubauer [8] realized 60% cures in the five years previous to 1951 and 66% cures in the three years previous to 1951, while Cosmetatos [9] obtained 70% cures in 374 operations performed between 1934 and 1948. Pereyra [10] felt that 81% of his 180 cases acquired excellent results and offered the intriguing information that the most usual period for reoccurrence of retinal detachment is in the months of June or July.

As mentioned earlier, it is our aim to continue urging patients who have been operated upon unsuccessfully to accept further surgery if it is at all feasible; we

have also been loath to decline surgery to what appears to be a "hopeless" case. Nonetheless, there is a number of patients who for various reasons did not submit to a second operation; if these patients are excluded from the series, the result is highly beneficial to the "statistics" and provides an unusually optimistic picture. As pointed out in Table 2, the over-all rate of cure then rises to 84.3%; the cure of secondary cases is lifted to 62.8%, and the chances of curing a patient who has not had previous retinal detachment surgery are 87.5%.

It is probably needless to point out that such a maneuver is of inestimable value to our, the physicians', egos, but it fails to improve the lot of the patient.

In 1930 Gonin [11] reported on his experience with about 250 patients with retinal detachment and concluded that cures should be obtained in 60% of *recent* cases. In our present series of cases, we were able to cure 204 patients of a total of 369 "primary" cases with a single diathermy procedure (55.3%); in addition to these patients there were 19 more who were cured by additional diathermy; thus, with diathermy alone we were able to cure 60.4% of our "primary" cases, a figure remarkably similar to that of Gonin (!).

TABLE 2.—*Cases Cured Compared with Total Number Operated On*

	All Cases, No.	Re-operation Refused	Cases Operated On	Cures, %
Total cases.....	440	46	394	84.3 (332/394)*
Primary cases....	369	26	343	87.5 (300/343)
Secondary cases..	71	20	51	62.8 (32/51)

* Number of cases cured/number of cases operated on.

In our series of "primary" cases, therefore, 60.4% of the cures were undoubtedly due to diathermy alone. Approximately 21% more cures were affected in patients who underwent one or more scleral resections in addition to diathermy directed at the tear. Whether this increase can be entirely attributed to the fact that a scleral shortening procedure was performed is problematical to some extent. For one thing, we have utilized scleral resection with less constraint during the past several years, and it is very likely that many of the patients who were cured with scleral shortening could have been cured by diathermy alone. In 1948, one of us (D. K. P.[12]) published a series of 100 successive cases in which diathermy alone was utilized; the rate of cure was 86%. A reasonable assumption is that many of the cases now seen are less favorable and that the more favorable cases are being operated on successfully by other physicians, who formerly might have referred them.

It is thus our impression that the great majority of recent retinal detachments can gain a lasting cure with diathermy alone but that with more and more complicated cases being encountered one is forced to resort to the ancillary procedure of one of the scleral shortening operations. This is in direct opposition to the conclusions of Moner and Simon,[13] who recently stated in an article regarding lamellar scleral resection, "It may be seen that the cases in which it is not recommended are the exceptions."

It is our feeling that we are in the best position to determine the causes of our own retinal detachment surgery failures by examining patients upon whom we

performed the initial operation and failed but were able to finally achieve a cure with further surgery. It is the purpose of this paper, therefore, to study these cases briefly and to offer some impressions, rather than to attempt any "statistical" analysis of our results.

In Table 3 it may be seen that there were 58 patients in the group of "primary" cases who needed more than one procedure to reattach the retina. It was felt that

TABLE 3.—*Results in Primary Cases*

	Cases	
	No.	%
Primary cases	369	
Those cured with a single operation	242	65.6
1. Diathermy alone	204	55.3
2. Scleral resection and diathermy	38	10.3
Those cured with multiple operations	58	15.7
Total cure of primary cases	300	81.3

TABLE 4.—*Primary Cases Not Cured by Initial Procedure (Fifty-Eight Cases)*

	Cases, No.
1. Original diathermy failure cured by repeat diathermy	19
2. Original diathermy failure cured by scleral resection	17
3. Original scleral resection failure cured by diathermy	7
4. Original scleral resection failure cured by resection	15

TABLE 5.—*Causes of Failure of First Operation*

	Original Diathermy Failure		Original Scleral Resection Failure	
	Cured by Repeat Diathermy	Cured by Scleral Resection	Cured by Diathermy	Cured by Another Resection
A. Original tear not closed	6	3	3	4
B. New tear developed	4	5	1	0
C. Another tear not found initially	4	2	0	3
D. No tear found	3	2	2	8
E. Insufficient drainage at first operation	2	0	1	0
F. Retinal shrinkage	0	1	0	3
G. Strands of contracting vitreous to retina	0	0	0	1
H. No apparent cause for initial failure	0	4	0	0
Total cases	19	17	7	15

TABLE 6.—*Probable Causes for Initial Failure in Cases Eventually Cured*

	Cases, %
1. Original tear not closed (16/58)	27.6
2. No tear ever found (15/58)	25.9
3. Developed a new tear (10/58)	17.2
4. Another tear not found initially (9/58)	15.5
Total	86.2

TABLE 7.—*Associated Findings in the Fifty-Eight Patients Not Cured by Initial Procedure*

	Cases, %
1. Aphakia	34.5
2. Myopia over −6.00 D.	18.9
3. More than two tears initially	22.4
Total	75.8

perhaps by reevaluating these patients upon whom we initially failed we might more readily understand why we were able eventually to achieve a cure for the patient. Categorically, these cases were divided into four classes (Table 4), depending upon which type of surgery was employed, and the most apparent cause for initial failure was then determined within each class (Table 5); Tables 6 and 7 present the over-all findings.

As noted earlier, we are immediately confronted by the fact that we have far too few cases from which to draw any statistically valid figures. All that we can offer under these circumstances are our personal impressions.

Very impressive to us is the fact that in these 58 patients whom we failed to cure with the first operation (but did cure with subsequent surgery) we had run afoul of three cardinal sins of retinal detachment surgery: failure to close the original tear (27.6%); failure to detect other tears present initially (15.5%), and failure to detect any tear at all (25.9%).

In 16 of the 58 patients the original tear was not closed; this was due to several factors. In some cases it was evident that technically our barrage of diathermy had not been complete and that there was a "leak" central to the tear. This can in large part be prevented if great care is taken to afford excellent exposure, so that the completed barrage is easily seen; removal of several of the rectus muscles and often the obliques is necessary to afford good exposure in many cases. When coagulating current is being used, care must be taken to assume a dry field for adequate choroidal reaction; this is less of a necessity when "cutting" current is utilized. In a few cases the vitreous adhesion to the flap of the tear was evidently sufficient to keep the tear open, thus allowing subvitreal fluid access to the subretinal space, and in turn this prevented the chorioretinal adhesions anticipated. If this is the picture of the fundus five to seven days postoperatively, it would perhaps be wise to reoperate at that time, performing a small scleral resection wth the intent of giving the vireous more "slack," thus enabling the pull on the retinal flap to be lessened. Perhaps a more frequent occurrence than can be ascertained from the figures shown is that often the drainage in the region of the tear is not sufficient to allow the tear to reach its bed of choridal reaction; the tear thus fails to reach the choroid while there is sufficient reaction to secure a firm attachment. More perforations at the time of surgery in the region of the tear will allow better local drainage, thus tending to avert this complication. If it is done only about seven days post-operatively, additional drainage at the site of the tear may enable it to settle.

In 15 of the 58 patients whom we eventually cured we never found a definite tear, and in 9 of the 58 patients we missed other tears that were present initially. The disposition and subsequent movement of the detached retina are not infrequently responsible for this lack of detection; some tears are hidden within the confines of a cleft between two bullae, and with settling of the retina the tear reveals itself. In some instances the settling of the retina will allow a tear hitherto unseen to move even further peripherally, thus escaping discovery. A tear in the retina that is only barely detached is difficult to see and often is noticed only by playing the ophthalmoscope light about so that by reflection the tear is made more noticeable. Haziness of the vitreous is still another factor that makes localization of tears difficult; settling of a vitreous hemorrhage after a few days of binocular bandages often allows a much clearer view of the fundus and the discovery of the retinal tears. It is perhaps pertinent to point out that whichever form of ophthalmoscopy is utilized, direct or indirect, neither insures discovery of retinal tears without the examiner's having mastered the use of each method and, having done that, learned to devote considerable time to the examination of the fundus.

In 17.2% of these 58 patients the initial procedure was successful in that the retina reattached itself everywhere; however, these patients then went on to develop a new tear, which led to recurrence of the retinal detachment. In all of these cases the new tear appeared in retina which at first had been attached, the appearance of the new tear varying from 7 weeks after surgery to 104 weeks postoperatively. The average time of the apparent development of the new tear was 12 weeks postoperatively.

Some of these new tears that develop are obviously due to further traction of the vitreous elsewhere, forming tears similar to the primary tear. Other new tears arise at the site of operative diathermy, frequently just at the limits of the diathermic barrage; it is not inconceivable that the diathermy itself produced

a vitreoretinal adhesion, eventually leading to a tear. There are tears in this category, however, that appear to be due to shrinkage of the outer layers of the retina, and with further contraction of the choroid and retina a retinal hole is produced. Some new tears appear diametrically opposite the former site of surgery; has the diathermy so affected the vitreous in these cases as to produce further shrinkage of its elements? This is certainly possible, and it is probably wise to keep in mind the potential action of the diathermy current upon the vitreous; frequent "coolings" of the globe with saline may help to prevent undue heating of the interior of the globe.

That this group of 58 patients was less disposed to success is possibly attributable to the fact that 75% of them (Table 7) were either aphakic, had moderately high mopia (over −6.00 D.), or presented themselves with more than two primary retinal breaks. The relatively greater "free play" of the vitreous in aphakic eyes can be construed as a force which would continually pull on the flap of a tear and thus keep it open, or also pull other portions of retina and in this manner produce other tears. Myopic eyes which gradually increase in their degree of myopia with the years tend to have exaggerated microcystic changes and are therefore more prone to develop multiple tears. With these thoughts in mind, we were inclined to perform scleral resections in 39 of these 58 patients.

Of the patients in this group of 58 whom we deemed candidates for primary diathermy, only 13.9% were aphakic, whereas 45.5% of those upon whom primary scleral resections were performed were aphakic. Likewise, no tear was discovered in 5 of the primary diathermy operations, whereas we failed to find a break in 10 of the patients who underwent primary scleral resection. It is evident, therefore, that we are more inclined to perform an initial scleral resection on those patients who are aphakic and in whom we are unable to discover an obvious break in the retina.

One could tease his imagination at considerable length by ruminating over the various figures set down in the several Tables included; however, there are admittedly too many imponderables and too few cases from which to form any new conclusions.

Comment

It is our impression that the majority of cases of retinal detachment can be cured by diathermy alone if it is correctly utilized. The various forms of scleral shortening procedure are invaluable in some circumstances, but they should not be regarded as a guarantee of success. Although lamellar scleral resection is unquestionably a safer procedure than a full-thickness scleral resection, the former is not at all an entirely innocuous procedure.

Scleral shortening operations should be regarded as auxiliary procedures in the treatment of retinal detachment. Cases with retinal shrinkage; aphakic patients in whom the detachment occurs shortly following the cataract extraction; cases in which the retina is obviously held off its choroidal bed by the vitreous; some cases of large oral disinsertions; cases previously operated on, with secondary retinal and vitreous changes; some cases of high myopia, and some cases of multiple tears can be regarded as candidates for a primary scleral resection. These cases do not form the majority of retinal detachments; they do, nonetheless, form a large number of cases seen by those who are particularly interested in doing retinal detachment surgery.

It is the slow and sometimes tedious work of increasing the percentage of cure that has made all of us attack more difficult cases. Having found some of the fundamentals of the cause and cure of retinal detachments, many men are now accepting the more complicated task of curing those patients whose plight is not only that of a tear in the retina but that of a disproportion between the area of retina and the area of choroidal bed. It is largely in this latter group, referred to earlier, that scleral shortening has its largest indication.

Conclusion

The greatest number of patients will be cured of their retinal detachment if it is first suspected by their doctor, then discovered, and then thoroughly examined not only for the primary tear but also for the "secondary" and "tertiary" tears. Failure to cure these detachments found early is usually due to a faulty sealing-off of the original tear, missing another retinal tear, finding no tear at all, or, in some instances, to the later development of a new tear. It has been our experience that these four factors most frequently are responsible for our own initial failures in retinal detachment surgery.

To secure the greatest number of cures, we must be prepared to operate more than once; in 369 cases not previously operated on, we were able to obtain a successful result in 15.7% more patients by operating again after an initial failure. The fact that we had seen the patients before any previous surgery probably allowed us to realize our own mistakes more readily and thus eventually cure the retinal detachment.

Summary

A group of 440 patients with retinal detachments is surveyed; 75.5% of them were cured. Of those patients previously operated upon elsewhere, we were able to cure only 45.1%. Of those patients who had not undergone previous surgery, we were able to cure 81.1%. An attempt to discover the commonest factors mitigating against a successful result appears again to revolve about the failure to completely close the original tear, the failure to detect the original tear or to find other initial tears, and the subsequent development of other tears after apparently successful surgery.

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Distribution Responsibilities of the Specialties Represented in the Scientific Assembly

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The National Society For The Prevention of Blindness states, "Every twenty minutes one more American loses the gift of sight. Some of this blindness is caused by disease, some by accident, and much by neglect."

We, its members, are the American Medical Association, and we believe it to be our responsibility to set the policies for the distribution of medical care for this country. The patient holds the doctor responsible in every category. We will provide the answers to the most complete and safe eye care possible, or others will try to. We can broaden the basic concepts that underlie safe distribution as we broaden our concepts of ever more effective treatment.

When the Michigan State Medical Society was developing Blue Cross and Blue Shield, we discovered that the name of "The Committee on Medical Economics" had to be changed to "The Committee on the Distribution of Medical Care." Doctors of Medicine were thinking it "unethical" that their attention should be given to anything other than the scientific. The development of the health sciences, research, and the distribution of scientific care is dependent on economic consideration, even of billions of dollars.

We discovered also that workable distribution required a command not only of economics, but of effective organization, of scientific analysis, of education, of legal analysis and procedure, of public information, of government, of political science, of insurance, and of journalism, in order to make applicable the nonprofit insurance principle in the distribution of health care.

Our experiences teaches us that when attention to enough distribution does not keep pace with scientific progress others take advantage of the situation; then, for reasons of lack of knowledge, avarice, political aspiration, or feeling of responsibility, these others tend to dilute the quality of both the science and the distribution of ophthalmology, or of any other Section of the Scientific Assembly. Increasing boldn ss in this regard, manifesting itself in subtle lobbying and legislation inimical to the best interests of the American people and contributing to the "one case of blindness every twenty minutes," basically brought about the special meeting in this Section last year with one thousand in attendance, with the results of which you are familiar. Some groups were demanding by legislation exclusive rights in certain segments of eye care—as if comprehensive and safe eye care can be broken up into segments.

There is but one criterion of exclusive right of any group in health care,

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and that is the exclusive right of every citizen as far as possible to the best available health care, and the measure of the need of that best lies in the fears, the hopes, and the longings in every American family from the President's down when the possibilities of tragedy strike in his family. We need only to do our duty, to present the sources of blindness as we know them, and the legislatures of our states will stand behind us. They want no blindness in their families at the hands of so-called "doctors" to confuse the issues. Our legislators are responsible to the people. One hundred forty thousand Doctors of Medicine, through their patients and through the American Medical Association, can inform the people.

Until it came to the attention of our Attorney General, a so-called "doctor" in Michigan was removing cataracts by the use of "drops." A patient of mine in his fifties was advised that he needed an operation for the removal of cataracts if he hoped to recover his vision. He wanted "treatment"—"drops," not surgery—and so he went to the so-called "doctor." His cataracts were removed all right, along with all of one eye and most of the other, and this one had gradual total loss of the little remaining light perception. "Yes, it was quite painful," he said. We had the drops analyzed by reliable testing laboratories, who reported "caustic soda." On the day of this writing a patient came to my office with one eye blind from glaucoma at the hands of a so-called "healer." There is a possibility of saving one-tenth of the vision in the remaining eye; I am not sure. I am speaking of typical experiences of all of us here today. It is a problem of responsibility, education, and leadership.

Something positive needs to be done to inform the people so that they understand the significance of the word "doctor." There is little doubt that this confusion contributes its share to blindness. No so-called "doctor" wants this to happen in his own family. Deception deceives all—even those who deceive.

On that day when Ophthalmology, looking to the future, set up the first American Board for the purpose of providing the highest possible educational preparation for the practice of ophthalmology, it forged the anchor of one of the most far-reaching safeguards to American health interests, and this graduate system has spread to every Section.

With this attainment, what can we do next in this Section to promote the most widespread distribution of eye care consistent with high quality, and under the direction of the Ophthalmologist, the Doctor of Medicine, in order that by any means the tragedy of the loss of vision of someone every twenty minutes may be reduced?

It would seem logical in the first place that enough Doctors of Medicine should be provided through enough medical schools to provide enough ophthalmologists. This is a subject for a paper in itself, and so I will confine my next few remarks to ways and means of aid to the ophthalmologists we now have, and this has to do with the subject of medical associates in general and ophthalmic associates in particular.

Several years ago the Michigan State Medical Society published a brochure that has gone through several editions, and there is now a moving picture based upon it, depicting twenty-four different technical occupations in aid to the Doctor of Medicine. This did not receive national help on the A. M. A. level; not everything can be done at 535 North Dearborn Street

without more help. And now the National Health Council, made up of fifty health organizations of America, has produced another, larger and more comprehensive, brochure, detailing one hundred fifty distinct opportunities in technical medical work to assist the Doctor of Medicine in the distribution of health care. On March 4, 1955, the *United States News & World Report* referred to this brochure, put out in cooperation with the Equitable Life Insurance Society of America. Last year The American Trade Association Executives "presented its Grand Award for State and Local Associations to the Michigan State Medical Society for having rendered outstanding service to the American Public, for its successful program entitled "Recruitment and Training of Medical Associates." We mention these to show the trend in public opinion and of public interest and aid in what we are trying to do on local levels and need to do on A. M. A. national levels.

Many ophthalmologists have proved that ophthalmic technicians can be trained, working always under the direction of the ophthalmologist, to expertly relieve him of much time-consuming detail and thus make him available to a greater number of patients. Precedence for such procedure has been established, as in the employment of orthoptic technicians; clinical laboratory technicians; dental hygienists, of whom there is a dearth, and trained persons who perform very many other laboratory procedures. The Brookings Institute states that dental care can be increased by 65%. Clinical laboratory technicians, dental hygienists, and orthopticians are spoken for before they are scarcely started in training in every new class. We need to include also technicians for field-taking, contact lens work, and refracting; optical technicians, technicians to work with eye-related reading difficulties in children, and others. It is estimated that the capacity of an ophthalmologist can be increased 100% by the use of technicians. Ophthalmology is probably the most technical of all specialties. As they were first in establishing the American Boards, ophthalmologists can give strong national leadership to a Medical Associates program through promotion of ophthalmic associates. As do all well-trained clinical laboratory technicians, they become expert by repetition, fascinated by the variety and significance of their findings, and scholastically interested and proud of their contribution to the physician's diagnostic records. One technician in training, determining fields for practice, in one year found two brain tumors in patients wholly without symptoms except for the need of glasses. There is reality to such a vocation. Ophthalmological therapeutics is increasingly expanding. Specialties are developing within this specialty.

There are parallels in every specialty. Anesthesia has become a highly trained Board specialty. However, there are not enough M.D. anesthetists, and so we have trained nurse anesthetists supervised by the medical anesthetist.

We now have 4700 Board-certified ophthalmologists in the United States. As the program of Medical Associates develops, if the capacity of the ophthalmologists can be increased by 100%, that would mean the equivalent of distribution under the direction of 9400 instead of 4700 ophthalmologists. Add to this the many ophthalmologists certified by the Board of Otolaryngology, but doing eye work also, and techniques for attack on glaucoma alone might be doubled.

As one who has tried the use of ophthalmic technicians trained by the ophthalmologist and working under the ophthalmologist, I want to say to you that it works. The people like it, and it is helpful in distributing more eye care and in satisfaction in more ways than can be detailed in this short paper. Those of us who practice in large centers and where residents are available need to realize that many good ophthalmologists in smaller centers have no resident and little intern help provided and are in need of technical aid. We need also to remember that the problems of some teaching centers are such that in training residents they want these residents to do all technical work themselves, to give them adequate experience. Teaching centers, however, can give aid to the training of ophthalmic technicians for the less favorably located ophthalmologists. It is understood that most of us after years of practice can not readily change to new systems, but we must look to all available means of aid to those who are in need and to the young men we are training to take our places.

I can say with emphasis that technicians trained by the ophthalmologist are superior in ability, accuracy, ethics, attitude, and approach to the patient, as compared with those with superficial training.

When a young ophthalmologist opens his office by himself in any community he is likely to have time to do everything himself, and he needs the experience, but as his work increases much can be delegated to laboratory procedure: Ophthalmic associates *is* laboratory procedure. The years of long, excellent, and expensive training given in developing a Board-certified ophthalmologist will neither economically nor scientifically allow him time to do every detail himself after his practice puts increasing demand on his services, or if he enters into a group practice where many patients are immediately turned over to him, any more than the chief engineers of our great automobile companies are allowed to fabricate every part that goes into an automobile. If those chief engineers did not have many technical assistants, very few of us could afford automobiles. Tool makers and other skilled technicians are trained in technical schools and on the job to provide highly technical assistance under the direction of engineers.

What is needed first in developing an educational program of medical associates is increased acceptance of the idea by ophthalmologists, which means the need for promotion through the Section of Ophthalmology of the A. M. A. to ophthalomogists and teaching institutions. The program needs trained personnel to go into our high schools and colleges to speak on the subject and to point out the needs and opportunities of colleges incorporating these subjects into their curricula. The largest demand for the Michigan brochure has come from vocational counselors in our schools and colleges. Many ophthalmologists would more readily adopt the laboratory method of employing ophthalmic associates if there were a supply of trained personnel. To train such associates in one's own office is an expensive procedure. To train them through educational institutions followed with experience in the ophthalmologist's office on a preceptorship basis, as is done in training orthoptic technicians, is practical.

If 85% of first contacts for eye care is at the hands of other than ophthalmologists, and if investigation reveals that this fact contributes to the loss of someone's vision every twenty minutes in the United States, the trend must

and can be reversed, to the satisfaction of all parties involved. No group wishes it to become public knowledge if their members are contributing to blindness. The better ones will cooperate to improve their status. Those who do not cooperate will through public education and through legislation become obsolete.

To actively aid in promoting a program of medical associates would take us into the fields of economics, education, science, law, government, ethics, distribution, and public relations. These, our A. M. A. headquarters can help us with. Given the facts and programs, the A. M. A. will be in position to aid in national promotion and leadership of medical associates, and our other major problems.

The people do not challenge us on the science of health care, but they do challenge us on the science of the distribution of health care. A superb job is being done in the science of medicine and in the public relations of the science of medicine. Yesterday it was potassium iodide. Today, penicillin. Tomorrow, something better. Our progress must be the same in distribution. What is the alternative to our assuming added methods of leadership? Simply this: to be out-voted.

We doctors talk much of private enterprise. Why do we not then respect the methods of private enterprise in scientific distribution of their products, without which they would fail. No multibillion dollar industry in America with equal responsibility to the consumers of its products would think of administering so great a business without sufficient administrative personnel. Blue Cross and Blue Shield are private enterprise for all concerned and deserve national coordination. Nationally these have not reached far yet into their great potential distribution possibilities.

We need our form of organization at A. M. A. headquarters. The present form needs no change, but we need an Executive Vice-President freed from minor duties, always responsible to the Officers, House of Delegates, and Trustees, to coordinate the administration of the health interests of 150,000,000 Americans. A resolution to this point is expected to be introduced at the current meeting of the House of Delegates. If we do not soon supply our own coordinator, there will be one in Washington.

The American Medical Association is the child and responsibility of the medical profession. We can accept the responsibilities of the health professions in the councils of our government and so in the nations in this atomic age with its potential to destroy the very health and life-saving objectives of the scientific assembly. There *is* a World Medical Association. The frontiers are as great as are the needs of health care in the preservation of freedom. This requires health care statesmanship.

In order that the American Medical Association may function to the extent of its responsibilities, it must be informed. I am of the opinion, from experience, that our delegate to the A. M. A. from this Section can not be adequately informed to carry our message into that very important legislative body, the House of Delegates, without more information than is allowed for by the time we have been in the habit of allotting in this Section to distribution. The delegate from this Section, or any other, has his hands full if he rises to the total position he assumes of representation and of leadership

in the highest health interests of the American people through our health "Congress," the national House of Delegates.

To help him we need to plan the distribution of ophthalmological care adequately and to set about, by every means at our command, in cooperation with the A. M. A. and the educational institutions of this country, to implement plans, or, let us have no doubt about it, we will find ourselves acquiescing in dubious trends instead of setting the trends in the distribution of eye care.

The medical profession has no authentic mouthpiece but the A. M. A. Individual physicians and our various Sections have their influence, but their national influence is represented by the A. M. A. Today our public relations are national. Any adverse publicity affects every Doctor of Medicine in America.

We physicians of all Sections are the A. M. A. The facts are that we are not furnishing to our A. M. A. adequate plans of procedure from the various Sections, nor is our A. M. A. organization at headquarters in position to digest and give adequate leadership to plans without more help from us. I commend to this Section the urgency of a commission, chosen by the Section, to study the problems of distribution within ophthalmology, and the urgent need of developing expanded educational programs in cooperation with educational institutions in furnishing to us trained technical personnel, that the science of ophthalmology may be supported in distributing more and better care under the ophthalmologist's direction.

We know the Doctor of Medicine must be in command of ophthalmology and its distribution if it is to be safe. Yet who will shape the future of eye care in America?—Government? Labor? Industry? the great Foundations? less broadly based groups?—or we ophthalmologists? The ophthalmologists of America represented here today can provide that answer.

208 David Whitney Building (26).

Luneburg Theory of Visual Geodesics in Binocular Space Perception

An Experimental Investigation

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Introduction

Luneburg [14] concluded that the metric of the space of binocular perception may be formulated in terms of negative Riemannian curvature, the curvature being constant. That is to say, he maintained the position that binocular space is hyperbolic in the sense of the geometry of Bolyai and Lobachevsky.

Luneburg developed his equations principally upon the basis of the Blumenfeld [3] alleys. Blumenfeld discovered that in addition to the well-known phenomenally parallel alleys studied by Hillebrand [10] and Poppelreuter [16] there is another alley, called by Blumenfeld the equidistance alley. The latter alley consists in this fact: If two rows of point-like lights are set up in a darkroom so as to appear straight, and parallel to each other, the various pairs of lights do not appear to be the same transverse distance apart throughout the alley's extent.

If binocular space were Euclidean, the parallel and equidistance alleys would coincide both phenomenologically and geometrically. But Blumenfeld found that, for his observers, the parallel alley lay inside the equidistance alley; this fact, according to Luneburg, means that the space metric for these observers was hyperbolic (negative Riemannian). If a case were found where the parallel alley lay outside (geometrically) the equidistance alley, then the observer's binocular space would be elliptical in the sense of the Riemann-Cayley geometry (K being positive).

No previous study has ever been made of parallel and equidistance alleys viewed under photopic conditions. The chief purpose of our investigation has been to test for Riemannian K-sign under photopic conditions and to compare results with those derived under scotopic conditions. For it must be borne in mind that the mathematical conclusions made by Luneburg were primarily based on Blumenfeld's experiment, which was carried out in a darkroom.

Historical Background

Blumenfeld founded his alley experiment [3] upon the work of Hillebrand,[10] whose investigation is a classic. Hillebrand reawakened interest in the vista problem, which had been discussed by Bouger about the middle of the eighteenth century, by Porterfield in 1759, and by Priestly in 1772.* Hillebrand used vertical

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I have had valuable discussions concerning the mathematics involved with Dr. Hermann von Schelling, mathematician at the Medical Research Laboratory. But it is to be distinctly understood that Dr. von Schelling is not to be deemed responsible for any of the mathematical statements or conclusions set forth in this article.

* Reference 4, p. 309.

threads as stimulus objects. Poppelreuter [16] repeated Hillebrand's parallel alley experiment, using vertical rods. Poppelreuter confirmed Hillebrand in all substantial respects: The loci of the sides of the parallel alley lie somewhere between the constant angle subtended by the fixed pair of stimuli most distant from the observer and the physically parallel lines running through these fixed stimuli at right angles to the vertical plane in which the stimuli lie.

Just what is the real significance of Blumenfeld's experiment? First, he was the pioneer in eliminating the observer's visual frame of reference by using small gas jet flames adjusted to a "blue" level, of faint intensity, in a darkroom. Second, he discovered that the sides of a parallel alley do not appear to be the same distance apart throughout the alley's extent. That is to say, psychological parallelism does not mean equidistance apart; by equidistance we here mean phenomenal equidistance.

The phenomenal parallels of Blumenfeld lay much nearer to the locus of the visual angle subtended by the pair of standard (fixed) stimuli than did the parallels of Hillebrand or Poppelreuter; this would be expected, because secondary criteria were eliminated by darkroom conditions. As Boring remarks, "This is, in Katz's sense, a reduction experiment."†

Blumenfeld's equidistance (frequently referred to as "distance") alley does not have sides phenomenally parallel to each other; this alley is built under the instruction that the apparent transverse distance between a given pair of stimuli (tiny gas jets) must be made equal to the apparent distance between the standard stimuli.

The outstanding significance of Blumenfeld's research consists in the fact that it seems to demonstrate that apparent parallelism does not carry with it apparent equidistance between the parallels, despite the fact of Euclidean plane geometry that two parallel lines are everywhere the same distance apart. Blumenfeld himself regarded this difference between parallel and distance alleys as merely paradoxical; he saw in this difference no psychometrical import for binocular perception.

But Luneburg, a mathematician, who became interested in the distorted rooms devised at the Dartmouth Eye Institute under the direction of Ames, recognized the importance of the Blumenfeld data for the geometry of binocular depth perception.‡

Luneburg was careful to point out that the hyperbolic visual metric cannot be considered as a certain conclusion until precise quantitative tests have been made: "We still assume that the visual space is a space of constant curvature. But whether hyperbolic, Euclidean or elliptic is decided by the experimental result of K being negative, zero, or positive."§ He also said that it "should be possible to find new directives for the design of binocular instruments such as binocular microscopes or range finders. The final test of our theory then rests upon the consistency of such applications."‖

When we undertake the construction of a distance alley, we are dealing with the problem of "size constancy," one of the more obscure questions in the history of psychology. Euclid was aware that apparent size does not follow the law of

† Reference 4, p. 296.
‡ References 14 and 15.
§ Reference 14, p. 104.
‖ Reference 14, p. 103.

the visual angle.¶ A large literature has grown up around this subject.# Hering (1879) distinguished between three kinds of size: (*a*) visual angle, or retinal size; (*b*) phenomenal, that is to say apparent, size; this does not follow the law of the visual angle; (*c*) estimated size, as determined by factors over and beyond bare sense-perception. There is no trouble encountered in drawing a distinction between (*a*) and either (*b*) or (*c*); the difficulty consists in distinguishing both in theory and in practice between (*b*) and (*c*). Hering said *scheinbare Grösse* for (*a*), *Sehgrösse* for (*b*), and *geschätzte oder gedachte Grösse* for (*c*).*

Boring is of the opinion that Holaday, who worked with Brunswik in Vienna, "has produced the best general analysis of the conditions that underlie this "constancey phenomenon'."† Holaday concluded that the nearest approach to "size constancy" is made when distance clues are provided; conversely, that the falsification of the impression of distance leads to a reduced impression of size constancy. This conclusion goes right back to Berkeley's thesis (1709) that size perception depends on distance perception.

Hardy and co-workers‡ carrying on the work of Luneburg, which was cut short by his untimely death, claim to have verified his hyperbolic theory. The Hardy experiments were conducted in a darkroom, using "points" of electric light for the stimulus configuration.

The human engineering aspect of the problem before us has to do with the possible relation of visual space curvature to various motor skills and capacities, wherein high degrees of precision are required of the operator in his visuomotor coordinations and adjustments. The Hardy study of visual goedesics was initiated under U. S. Navy auspices; it was believed that such a study might reveal relationship of the curvature (K) constants of a number of observers to their mechanical abilities. "The possibility that a high correlation of mechanical abilities (in drivers, pilots, steersmen, gun sighters, etc.) to the values of K could be established was a principal motivation in undertaking this study."§

Experimental Design

The main technical problem involved was to devise an equipment which would transform the Blumenfeld experiment into terms of daylight vision.

Equipment—The stimulus-pairs were Munsell N-1 paper squares, 5/16 in. on a side. These squares were glued to rectangular methacrylate (Plexiglas) strips $10\frac{1}{2} \times \frac{5}{16} \times \frac{1}{16}$ in.; each strip was clamped vertically into a weighted wooden block grooved to slide along a meter stick set transversely on a table. The transparent methacrylate used was colorless, with a transmission of 92% in the visible range.

Each black square was at the top of a methacrylate strip, the strip being adjustable so that it could be set at such height as to make the top horizontal edge of each square lie in a common horizontal plane. The blocks into which the strips were fastened could be set at any position on the meter stick by means of a thumbscrew.

Distance of furthest (fixed) stimulus-pair from eyes was 350 cm.; transverse

¶ Reference 4, p. 309.
# Reference 4, pp. 308-311.
* Reference 4, p. 309.
† Reference 4, p. 298.
‡ References 7 and 8.
§ Reference 8, pp. 54-55.

distance between the fixed pair being 20 cm. The fixed pair were glued to the white cardboard background.

The stimulus squares were so set that a direct reading of the meter sticks gave a highly precise measure. We used seven stations, at the following distances from the observer's eyes as measured along the median line: 65.7, 85.6, 111.2, 145.4, 195.1, 266.1, and 350.0 cm. Station 1 was at 350 cm.

Observer's view of the table top was prevented by appropriate screening. An adjustable chin and head rest permitted obtaining the desired angle of vision with respect to the plans of the stimulus squares. Calibrations of the experimental set-up were frequently made. Illumination was furnished by an overhead L. C. Doane Co. fluorescent Luminaire, 9000-S6401, 73818, Rev. 4-Type, JF-31B; two 8-watt lamps, G. E. Daylight, furnished just the right illumination: Brightness of white background was about 10 fL.

Procedure.—Each observer completed the parallel alley task before undertaking the construction of the distance alley. Instructions for building the parallel alley follow:

"You see a pair of black squares in the white background.

"I ask you to instruct me to set other pairs of squares so that, when they are all set, you can confidently say that (1) the right and left hand arrays of squares *appear* to be parallel to each other and that (2) each array of squares *appears* to lie in a straight line.

"The two lines of squares must be made to appear as if they could never meet no matter how far they might be extended in front of or in back of you. Be careful to avoid even a trace of the appearance you see in railroad tracks which converge in the distance.

"Be sure to view the alley formed by you as a *whole*. If you find at any time that you become unable to grasp the configuration of squares as a *totality*, so inform me.

"You must use *both* eyes at all times when you are making the alley. Let your gaze wander freely over the region of the squares."

Instructions for constructing the equidistance alley were as follows:

"You see a pair of black squares in the white background.

"I will now show you a second pair of squares. You see that the two pairs of squares appear to be at different distances from you. You are to instruct me to set the pair of squares last shown you in such a way that the *apparent* distance between these squares is the same as the *apparent* distance between the fixed pair of squares first shown you; they are to be set symmetric to the median.

"Do not reason about the situation, do not try to estimate width. Simply *sense* the apparent widths as quickly as you can and make your judgment *while holding your depth-perception attitude.*"

Instructions were read by the observer and thoroughly discussed with the examiner. The greatest care was taken to insure that the observer carried out the instructions at all times.

Observers.—There were four observers, including the examiner. Three of the four observers were psychologists, the other observer being unversed in experimental psychology. The observers will be identified thus: P.C.S., C.C., G.L., T.S.

Darkroom Alleys.—T.S. was conducting his own experiments on the Blumenfeld alleys under darkroom conditions at the time of our experiment; his work

was performed at the American Optical Company, Southbridge, Mass. Thus, T.S. was tested both under his and our illumination conditions; P.C.S. was likewise tested under both conditions.

Results

Tables 1, 2, 3, and 4 show that for three observers the parallel alleys lie outside the distance alleys; these observers operated strictly under the experimental

TABLE 1.—*Observer P.C.S., White Light*

Station	P-Alley (Cm.)	D-Alley (Cm.)	D-Alley (Nonunitary) (Cm.)
1	10.0	10.0	10.0
2	9.0	8.2	9.3
3	8.2	6.3	8.5
4	7.5	5.6	7.9
5	7.1	4.6	7.8
6	7.2	4.8	7.3
7	6.8	5.1	8.2

TABLE 2.—*Observer C. C., White Light*

Station	P-Alley (Cm.)	D-Alley (Cm.)
1	10.0	10.0
2	8.8	8.3
3	7.8	6.8
4	7.0	6.3
5	6.5	5.8
6	6.8	6.0
7	6.6	5.5

TABLE 3.—*Observer C. L., White Light*

Station	P-Alley (Cm.)	D-Alley (Cm.)
1	10.0	10.0
2	9.6	9.0
3	9.4	8.2
4	8.9	7.3
5	8.7	6.7
6	8.8	7.6
7	8.9	7.8

TABLE 4.—*Observer T. S., White Light*

Station	P-Alley (Cm.)	D-Alley (Nonunitary) (Cm.)
1	10.0	10.0
2	8.7	10.8
3	7.1	9.5
4	5.8	8.4
5	4.9	8.8
6	4.7	9.0
7	4.3	9.4

instructions. For them, binocular space is Riemannian-positive, i.e., elliptical. There is not the slightest evidence indicating a Euclidean visual space.

The measures given in the Tables are for the right side of the alley only, the two sides being substantially symmetrical.

For T.S., the binocular metric in our white-light situation is prima facie hyperbolic, i.e., Riemannian negative; his parallel alley runs inside of his distance alley.

The dihedral angle formed by intersection of the stimulus plane and the plane running through the observer's pupils to Station 1 is approximately one degree. Let us designate any angle of intersection as θ.

Note that the non-unitary D-alleys (distance alleys) in Tables 1 and 4, lying outside of their associated P-alleys (parallel alleys), give presumptive evidence of a hyperbolic metric. "Nonunitary" here means that the two pairs of apparently equal tranverse distances were not apprehended by the observer as a unified depth-Gestalt: This fact is crucial to an evaluation of the Luneburg theory.

Tables 5, 6, and 7 show data derived from the darkroom alley experiments conducted at the laboratories of the American Optical Company; in these Tables, θ equals approximately 2.3 degrees.

TABLE 5.—*Observer P. C. S., Darkroom*

Station	P-Alley (Cm.)	D-Alley (Cm.)
1	10.0	10.0
2	9.4	9.2
3	8.7	7.2
4	8.2	5.4
5	7.5	4.8

TABLE 6.—*Observer T. S., Darkroom*

Station	P-Alley (Cm.)	D-Alley (Nonunitary) (Cm.)
1	10.0	10.0
2	8.8	10.5
3	7.6	10.2
4	7.0	9.6
5	5.7	13.3

TABLE 7.—*Observer T. S., Darkroom**

Station	P-Alley (Cm.)	D-Alley (Nonunitary) (Cm.)
1	10.0	10.0
2	11.1	11.3
3	11.2	11.4
4	10.2	12.3
5	8.1	12.5

* In this Table, $\theta=0$.

Comparison of Tables 6 and 7 reveals that raising of the eye-level above the plane of the stimuli is associated with a wider spread between the P-alley and D-alley, but the mapping is presumptively Riemannian-negative in both Tables.

Only five stations were available in the darkroom observations.

T.S. reported that he built his D-alleys by comparing apparent transverse distances under an *Einstellung* which regarded the two pairs of squares as lying in two different vertical planes which were not unified, integrated, as a depth-Gestalt. He seemed entirely unable to compare any two transverse distances while maintaining a depth attitude. That is to say, he admitted that he could not follow the explicit instructions on this point. The other observers had no difficulty in following the instructions on the matter of depth attitude. Thus, T.S. was avowedly nonunitary in his attitude when forming the D-alleys, and the question arises whether this attitude was basic in producing his so-called hyperbolic metric.

P.C.S. was able to obtain a hyperbolic metric by deliberately assuming the nonunitary attitude in formation of the D-alley (Table 1, last column); his nonunitary D-alley lies outside of his P-alley.

Comparing Tables 1 and 4 with Tables 5, 6, and 7, it is clear that the algebraic sign of the Riemannian K was not affected by illumination conditions. P.C.S. is Riemann-Cayley-elliptical under either white light or darkroom conditions; T.S. is Lobachevskian hyperbolic (prima facie, at any rate) under both conditions.

In our white-lighted alleys it is true that there are various empirical depth-perception clues. One might suppose that in the darkroom alleys, where empirical clues are absent, the depth experience would be markedly less than for the photopic alleys. But for P.C.S. the depth effect in the darkroom alleys at the American Optical Company laboratories was striking, far surpassing the depth effect he had expected to see. In fact, although the stimulus brightnesses of the light points were most carefully made apparently uniform by P.C.S., he could not readily perceive the pairs of light points except as strongly bound together in depth relation.

Discussion

No trace of zero K (Riemannian) having been found in our experiments, we are unable to accept as valid Fry's contention‖ that binocular space is Euclidean.

Hardy and co-workers state: "The most striking evidence that visual space is non-euclidean lies in the distinction in visual perception between apparently parallel straight lines and curves of apparent equidistance. This difference was first reported by Blumenfeld."¶

When the observer is instructed to construct a parallel alley, the sides to appear straight, he is building geodesics. A geodesic may be defined as (1) shortest line or (2) straightest line; definition (1) is that of metrical geometry. Definition (2) is usable both in geometry and in psychology. "Straightness" in a parallel alley is a phenomenological quality, closely akin to a bedrock sensory quality, and, mathematically, the "straightest" line "is not an absolute property of the surface, but depends on the way the surface is imbedded in space."# In a parallel alley, the "shortest" line would be a matter of inference; but the "straightest" line is a matter of direct observation.

In an article by Hardy and co-workers* the K-constants of 15 observers were reported; of these, 6 Ks are positive, indicating elliptical space, the other Ks being negative. However, in the final report issued by Hardy and co-workers the six cases of positive K are not even mentioned[8]; only two sets of alley loci are presented, both representing negative K.

Since only one of our four observers was hyperbolic (prima facie), the others being elliptical, the question at once presents itself as to whether the observer (T.S.) who presumptively manifested negative K rigorously followed out the instructions. The answer is that he did not. We know that the other three observers did scrupulously follow the instructions.

Close questioning of T.S. revealed that when he constructed his distance alley he compared the two transverse distances as separate configurations, not tied together in a depth-Gestalt. Thus, he viewed the two transverse distances in a

‖ References 5 and 6.

¶ Reference 8, p. 20.

Reference 9, p. 221.

* Reference 7, p. 10 of reprints.

nonunitary manner, never as integrated into an over-all whole. The instructions explicity require that the observer make his judgment of apparent transverse equality while holding the depth-perception attitude. T.S. formed his parallel alley correctly enough: He made his settings while regarding the situation as a whole. But he shifted his attitude to a purely analytic one when building the distance alley. An alley cannot be an alley unless it possesses a depth characteristic. Thus, it is plainly evident that T.S. built the two alleys under entirely different attitudes, namely, the totalizing and the analytic. His distance "alley" cannot properly be called an alley at all.

Neither Blumenfeld nor the Hardy group constructed their distance alleys under instructions to the observers to maintain the depth perception attitude or set. Luneburg had the key to the solution of the problem of binocular space metric in his hands, but he threw away the key by failing to recognize that the P-alley, constructed under the totalizing, Gestalt attitude, cannot validly be compared to the D-alley built under the partializing, nonunitary *Einstellung*. The D-alleys we find in the experimental literature are not phenomenal realities but psychological abstractions, because depth is of the very essence of any alley.

The P- and D-alleys of P.C.S., C.C., and G.L. were built upon the firm foundation of depth perception and upon the tenacious adherence to an over-all totalizing attitude; positive Riemannian K resulted. We must carefully note that when P.C.S. shifted his attitude to the nonunitary one while constructing a D-alley he manifested negative K (Table 1, last column). Now, which is the true metric for P.C.S., hyperbolic or elliptic?

The Luneburg hypothesis depends upon the tacit assumption that the P- and D-alleys are validly comparable. We maintain that they are of entirely different psychological constitutions, and hence noncomparable mathematically: The alleys belong to utterly different universes of psychological discourse. The D-alley is not a phenomenal alley: this is the crucial point overlooked by Luneburg. It is our conclusion that the non-Euclidean metric of T.S., as evidenced by his settings in both the daylight and the darkroom situations, cannot be correctly defined as that indicative of a hyperbolic geometry; rather, his metric may be characterized as quasihyperbolic or pseudohyperbolic.

We not only have established the nonhyperbolic nature of binocular space for our observers but we have also ascertained the fact that the sign of the Riemannian curvature does not change for a given observer under change of illumination conditions (darkroom or white light), for the values of θ used in this experiment. Some time after we had formulated our views on the Luneburg hypothesis, we came across some notes by Renshaw, who states: "But of course the question arises: how much does one artificialize the situation by elimination of normal field or peripheral seeing conditions? The point is debatable"†; he also says: "The question of the proper metric for binocular space remains open."‡

Luneburg, although he originated and strongly favored the hyperbolic hypothesis of binocular space, does not seem to have been completely dogmatic about the matter§; also, it must be borne in mind that he died before he could have the opportunity to consider the mathematical implications lying in the phenomenology of recent work. Deductive logic has played too large a part in Luneburg's hypothesis: He was a mathematician, not a psychologist. Luneburg's followers have

† Reference 17, p. 45.
‡ Reference 17, p. 45.
§ Reference 14, p. 104.

carried on the work he began with great zeal, with almost a fanatical fervor; perhaps they* have manifested dogmatism more acutely than did Luneburg.

Visual space is a hypothetical space; it is not a physical space. Luneburg's task was to determine the mapping of physical space into visual space and thereby be in a position to characterize the visual space. With the assumption of a constant curvature, K, then Riemann's differential line element expresses the metric of any space. The metric of a space determines all the properties of a space. Spaces represented by the Riemann differential line element are the only spaces in which localization and form are not correlated.

Only by the assumption of point-sources of light for stimuli in a darkroom can we legitimately apply the technique of differentials to the determination of the mapping function. Where gross stimuli are used, as in our experiment, the use of differentials must be replaced by the theory and practice of finite differences.

Hilbert states: "An effective description of physical reality must be based not on ordinary Euclidean geometry, but on a more general Riemannian geometry."‖ The same may be said of phenomenal reality.

The "size constancy" phenomenon is the basis upon which the distance alley is derived. This phenomenon is not yet clearly understood. According to Boring, Holaday,[11] who worked with Brunswik in Vienna, "has produced the best general analysis of the conditions that underlie this 'constancy phenomenon'."¶

Recent studies on the Luneburg hypothesis are those by Bank.# Of course Koffka's book [13] has become a modern classic on configurational principles; these principles must be understood by anyone investigating the Luneburg hypothesis. As Boring states the case: "It is to Gestalt psychology that the modern psychologist turns for his systematic framework when he deals with perception."*

Main Conclusions

This experimental investigation of both parallel and equidistance alleys is the first one to be made under white light conditions. The following conclusions have been drawn:

No evidence has been found indicating a parabolic (Euclidean) metric for binocular space.

Binocular space does not evidence the hyperbolic metric for the observers used in this experiment. This fact contradicts Luneburg's hypothesis that negative Riemannian constant curvature characterizes binocular space.

Three of our four observers evidence the metric of elliptic Riemannian space, the curvature being positive.

A fourth observer, who presumptively satisfied the Luneburg conditions for the hyperbolic space metric, should rather be designated as of quasihyperbolic or pseudohyperbolic type.

The algebraic sign of the non-Euclidean metric is not affected, so far as our data reveal, and under the values of θ used, by the differences between white lighted and darkroom conditions.

‖ Reference 9, p. 172.
¶ Reference 4, p. 298; Reference 12.
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Clinical Notes, New Instruments and Techniques

A JAPANESE PROJECTOCHART SLIDE

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IT HAS been evident for many years in my practice in Honolulu that in order to properly test the vision of Japanese who are not familar with English characters a new type of test chart similar to that currently used (Snellen) would be necessary.

Maintaining the requirements of Snellen type, i.e., that it subtend an angle of 5 minutes of arc, presented a considerable problem, owing to the variations in the thickness of Japanese characters, particularly those of the Hiragana and Kanji varieties. These characters of the Katakana division (elementary), however, lent themselves better, to this use, and by modifying these characters slightly, so as to not lose their identity, it has been possible to make them conform to an angle of 5 minutes of arc uniformly. The result is the slide illustrated.

Characters varying from 20/400 to 20/15 are now available in step-down sizes, and a minimum of repetition will thwart memorization of this chart. Character separation is sufficient to permit the use of the bichromatic test currently employed by ophthalmologists.

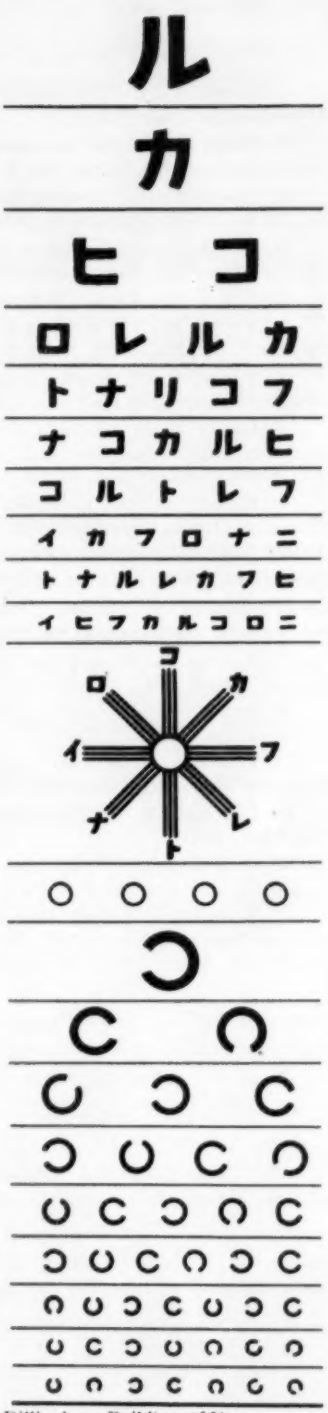
The astigmatic dial has been simplified by eliminating excessive radii, and instead of identification of each radius by a number, such as "11," each one is now conveniently identified by a Japanese phonetic sound such as "fu," "ka," etc. Elimination of excessive radii improves the use of the cross cylinder with this test chart.

Below the astigmatic dial are four standard colors—red, blue, green, and yellow—which meet the requirements of lantern red, blue, green, and yellow.

The illiterate chart goes one step further in simplification, presenting the subject being examined with only a circle with a "break" in it. The patient is asked simply to state whether the "break" is above, down, to the right, or to the left.

This new slide will make the recording of vision in Japanese subjects not familar with English characters simple and accurate. The characters representing sounds can be easily learned and memorized by any ophthalmologist in a few minutes.

Distribution of this slide will be made by the American Optical Company, of Southbridge, Mass.



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Annual Reviews

OPHTHALMIC PHARMACOLOGY AND TOXICOLOGY

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DURING the period April, 1955, to April, 1956, there have been published several hundred articles concerning pharmacology and toxicology of the eye. It seems that the most popular pharmacologic subject has been the influence of drugs on intraocular pressure, with a predominant interest in the action of acetazoleamide (Diamox). Previous peaks of preoccupation with antibiotics and corticosteroids seem to have passed. Under the heading of toxicology, numerous and varied observations have been added to the literature, but no one subject has surpassed in interest or importance the role of oxygen in the development of retrolental fibroplasia.

In reviewing this period it has been my intent not to provide an exhaustive or all-inclusive compendium but to summarize and correlate the developments of the past year in a simple and convenient form.

Ophthalmic Pharmacology

Influence of Drugs on the Intraocular Pressure.—World-wide interest in the influence of acetazoleamide has been evidenced by the flood of articles which have appeared in the ophthalmic literature during this second year following the introduction of this drug into ophthalmology. This interest has been aroused not only because because of the clinical usefulness of acetazoleamide in management of glaucoma but because it has seemed reasonable to expect that the mode of action of this drug in the eye may be completely elucidated in the near future, and that in the process much may be learned concerning the mechanism of formation of the aqueous humor. The mode of action has not as yet been completely elucidated, but progress in this direction has been made, despite occasional disagreement and misunderstanding. Clinical evaluation of the drug has been relatively simple, yielding the same general conclusions in the hands of numerous different investigators. In fact, so many reports have appeared saying essentially the same thing that these will not be considered or listed individually. It has generally been agreed that acetazoleamide is valuable for rapid alleviation of the acute glaucomas but that for prolonged control of chronic glaucoma it would be much more useful if it did not so commonly induce anorexia, weight loss, and fatigue. Paresthesias of hands, feet, and face occur even more commonly, but these are less objectionable to the patient and are readily reversible when the medication is discontinued. Remarkably few instances of serious complications have been reported. Possibly owing to the fact that acetazoleamide, unlike the bacteriostatic sulfonamides, has no benzene ring, it has rarely been reported to cause organic damage. Although this drug has been widely used for several years, there has been attributed to it in the literature only one case each of agranulocytosis,[82] thrombocytopenic purpura,[92] and microscopic renal lesions.[32]

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Clinical applications of acetazoleamide in ophthalmology other than for control of glaucoma have been made for relief of postoperative collapsed anterior chamber and for corneal edema secondary to endothelial dystrophy. In the case of failure of the anterior chamber to reform as soon as expected following cataract extraction or filtration operations for glaucoma, the impression has been obtained clinically that acetazoleamide has helped in the restoration of the chamber, yet no series of controls without the drug have been compared.* Since the conditions contributing to flat anterior chamber are so varied, and so often the chamber reforms spontaneously, it seems that large series of cases with and without the drug must be compared in order to evaluate reliably the suspected beneficial action. There has not so far been a definite rationale for this application of acetazoleamide such as there has been for its application to the treatment of glaucoma. Similarly, the trial of acetazoleamide in treatment of corneal edema seems to have been prompted by hope rather than science, and in this case the hope appears to have been justified by the results.[100] Oral administration of only 250 mg. every one or two days is reported to have relieved significantly in 18 out of 22 cases the edema of the corneal epithelium which is associated with endothelial dystrophy. The effect was judged by biomicroscopic examination and by measurement of improvement of visual acuity. In some instances the improvement has been maintained for at least 11 to 13 months. Since corneal edema from endothelial dystrophy does not ordinarily improve spontaneously, the objective evidences of benefit in this considerable proportion of cases appear significant. The eyes in these cases were not glaucomatous, and it is assumed that the intraocular pressure was not significantly reduced by the treatment, but this has not been established by measurement. The mode of action in these cases is not known. It is interesting to note in this connection that another diuretic drug, meralluride (Mercuhydrin), also had some beneficial effect in four patients, although it differs from acetazoleamide in several respects and is not an inhibitor of carbonic anhydrase. It would be helpful in elucidation of the mode of action to know whether acetazoleamide benefits corneal edema when applied topically.

Experimentally, the manner in which acetazoleamide affects the eye to cause a lowering of intraocular pressure has been analyzed to the point where it is generally agreed that the lowering of pressure results from a decrease in rate of formation of aqueous humor, but how the decrease in formation is brought about has been only partially elucidated. The decrease in rate of formation of aqueous humor has been ascertained by use of tonography and rate of change of concentration of fluorescein in the aqueous humor in human and animal eyes and by *p*-aminohippuric-acid-disappearance time in animal eyes.† Results obtained are concordant with those of previous studies and with the hypothesis which originally led to the trial of acetazoleamide for relief of the pressure in glaucoma. A more unexpected and remarkable observation has been that the facility of outflow of aqueous humor may become impaired when the rate of formation is depressed by acetazoleamide in human and rabbit eyes.[10] These changes are antagonistic in their influence on the intraocular pressure; accordingly, the effect of acetazoleamide on the pressure may in certain eyes be limited because the suppression of formation of aqueous is partially compensated by diminution of facility of outflow. These conclusions were drawn from measurements by means

* References 2 and 108.

† References 10, 56, and 63.

of tonography on human and rabbit eyes and by means of fluorescein in rabbit eyes. In normal human eyes the impairment of facility of outflow is reported not to be manifest during the first 2 to 4 hours following administration of acetazoleamide, when the rate of formation and intraocular pressure are at a minimum, but to become evident at a later stage, 6 to 24 hours after medication, as the rate of formation is returning to normal. In rabbit eyes the change in facility of outflow is said to occur at a much earlier stage.

In experimental work on acetazoleamide in rabbits a difference in response of various animals has become well recognized, some animals having a negligible change in intraocular pressure and others a definite lowering of intraocular pressure promptly following systemic administration of the drug.‡ Unresponsive rabbits are found to be gradually rendered responsive by increasing the amount of sodium chloride in the diet during several weeks, or by administration of adrenal corticosteroid hormones which influence salt retention they may be rendered responsive to acetazoleamide within two or three hours.§ The basis for this effect remains obscure, but evidence has been presented that reactive and unreactive rabbits may not differ in degree of suppression of formation of aqueous humor but only in whether or not they have compensatory alterations of facility of outflow.[10] This remains to be further tested. This reversible secondary influence of acetazoleamide on facility of outflow has not yet been reported from more than one laboratory, all previous conclusions having been that the facility of outflow was not altered by acetazoleamide. However, because of its complex nature and the delay in its appearance in human eyes this phenomenon may well have gone undetected in earlier studies. A reversible change in facility of outflow secondary to a change in rate of formation tending to keep the pressure constant has also been noted when the ipsilateral carotid artery has been ligated in experiments in rabbits, and this sort of phenomenon may be a manifestation of a homeostatic mechanism within the eye.‖ More observations may be expected, since this has become a popular subject among investigators.

Investigations of the chemical and enzymatic aspects of the pressure-lowering action of acetazoleamide have mostly been aimed at testing mechanisms which might fit in with current concepts of how the aqueous humor is formed. From earlier evidences that there is an energetic mechanism in the ciliary body which yields a fluid more alkaline than the blood, and from the fact that there is carbonic anhydrase at hand to facilitate a shift of carbon dioxide from blood to the newformed fluid, it has been expected that inhibition of the enzyme by acetazoleamide would result in a decrease in the rate of entry of carbon dioxide and accordingly a decrease in the resultant bicarbonate concentration in the aqueous humor. This is indeed found to be the case, at least in animal eyes, by the majority of investigators.¶ Occasionally results have been reported which seem to be discordant but actually may not be. For example, in one report in which the bicarbonate concentration of the aqueous humor was claimed not to diminish under the influence of systemically administered acetazoleamide it has become apparent from examination of the methods that it was actually the carbon-dioxide-combining power and not the bicarbonate concentration of the aqueous which was determined.[36]

‡ References 8, 10, and 56.
§ References 10 and 56.
‖ References 26, 27, and 57.
¶ References 9, 55, and 64.

A seemingly much more serious discrepancy between what has been expected and what has been observed is a finding which has been repeatedly confirmed, that application of acetazoleamide to the eye itself does not cause a fall in intraocular pressure even though the carbonic anhydrase activity of the ciliary body and iris appears to be reduced to an undetectable level.# These circumstances naturally have raised suspicions that the ocular effects of systemically administered acetazoleamide may be secondary to actions elsewhere in the body, but the fact that the intraocular pressure begins to decline within minutes of intravenous administration of the drug and that the effect on the eye is not altered by nephrectomy argue for an action within the eye.[9] As a compromise which might bring experimental findings into concordance, it seems worth considering that with respect to the eye the principal function of carbonic anhydrase may be to facilitate the release of carbon dioxide from the blood and thereby make the carbon dioxide readily available for diffusion across the blood-aqueous barrier into the eye. If the availability from the blood stream is the prime factor limiting the rate of entry of carbon dioxide into the eye, then it may be that it is not the activity of carbonic anhydrase in the thin layer of tissue constituting the blood-aqueous barrier but the activity of the blood itself which limits the rate of entry of carbon dioxide into the eye. This would explain the failure of local application of acetazoleamide to alter the intraocular pressure, since the fresh supply of blood continually entering the ciliary body would presumably have normal carbonic anhydrase activity and normal availability of diffusible carbon dioxide despite inhibition of the enzyme in the tissue. According to this suggestion, only by imposing a limitation on the availability of carbon dioxide from the blood, as by inhibiting the carbonic anhydrase of the blood itself, would the rate of diffusion from blood to new-formed aqueous be reduced. This possible relationship might be analyzed by examining the influence upon intraocular pressure of factors which alter the availability of carbon dioxide from the blood by mechanisms other than variation of carbonic anhydrase activity. Pertinent observations have come from examining the influence of acidosis induced by administration of ammonium chloride to rabbits. Under these circumstances the bicarbonate content of the blood is reduced as a result of respiratory loss of carbon dioxide, and the rate of formation of aqueous humor as measured by fluorescein appearance time is slowed.[62] Clinically, it would seem that there should be good opportunity to develop this subject, as for example in connection with acidosis of diabetes, where ocular hypotony has long been noted but not adequately explained.

Another problem in elucidating the action of acetazoleamide, and with it the fundamental details of how the aqueous humor is formed, is the consideration of how the volume of aqueous humor entering the eye can be influenced by the rate of entry of carbon dioxide. It has generally been accepted that the volume of aqueous humor formed per minute is related to the number of osmotically active particles (ions or molecules) entering the eye per minute, and that the rate of entry of water is so fast that it dilutes these particles to a concentration osmotically approaching, but not quite reaching, that of the blood. From this concept it is to be expected that decreasing the rate of entry of osmotically active particles without altering the fundamental mobility of water would result in formation of a smaller volume of aqueous, and this aqueous would more closely approach the osmotic level of the blood. Estimation of the ionic concentration

References 24, 31, 37, 38, and 94.

of the aqueous humor from electrical conductivity measurements has in fact shown that the concentration of ions is decreased under the influence of acetazoleamide.[109] The problem remains, however, to explain how altering the rate of entry of carbon dioxide could alter the total number of osmotically active particles in the aqueous humor. It has been postulated that carbon dioxide, or carbonic acid formed therefrom, simply reacts with hydroxyl ions which have been generated by the oxygen-transporting secretory mechanism of the ciliary epithelium to form bicarbonate ions. Conversion of hydroxyl ions to an equal number of bicarbonate ions would not, however, in itself be expected to change the osmotic pressure. Any consequence of the tendency of these anions to associate with cations to yield an osmotically less active solution would probably be in the direction of decreasing osmotic activity with increasing conversion of hydroxyl to bicarbonate. If the opposite were the case, it might help to explain the influence of acetazoleamide on intraocular pressure. It seems, however, that to account for the diminished rate of formation of aqueous humor which is caused by acetazoleamide some additional factor must be considered. It would, for instance, be pertinent to know whether failure of conversion of hydroxyl to bicarbonate has a suppressing influence on the rate of generation of hydroxyl ions by the ciliary epithelium, but this may be difficult to determine. At least the basicity which governs the carbon-dioxide-combining power of the aqueous does not seem to be appreciably diminished.[86]

The secretion of ascorbate does not appear to be influenced by acetazoleamide in a manner to account for the observed alteration of intraocular pressure; the concentration may actually be increased in the aqueous humor rather than depressed.[93] Acidosis induced by ammonium chloride has the same effect on ascorbate as does acetazoleamide.[63] An intriguing possible reciprocal relationship between ascorbate and bicarbonate in formation of aqueous humor has been suggested by an observation that ascorbate could under special circumstances counteract the influence of acetazoleamide on the pressure in the eyes of rabbits.[26]

Looking elsewhere in the mechanism for formation of aqueous humor for influences of acetazoleamide which might explain its pressure-lowering action, several authors have examined the rate of entry of sodium and its steady-state concentration in the aqueous humor and have found them to be uninfluenced.* On the other hand, the concentration of potassium has been shown to be significantly decreased in the aqueous humor of rabbits three hours after intravenous administration of acetazoleamide, and this may prove to be a valuable lead.[25]

Despite the large portion of the literature recently pre-empted by acetazoleamide, a great many reports have appeared concerning the influence of a wide variety of other substances on the intraocular pressure during the past year. In fact, some impression is obtained that the very success of acetazoleamide, as well as progress in investigative methods, has been a stimulus to the examination of other compounds.

Sympathomimetic drugs have been well studied by the use of tonography and photometric measurement of rate of disappearance of fluorescein from the anterior chamber in normal and glaucomatous human eyes.[112] Lowering of intraocular pressure following topical application of epinephrine is found to be greatest about 12 hours after its administration; the lowering of pressure is accomplished by decreasing production of aqueous humor and not by change in facility of out-

* References 25, 47, and 55.

flow. Arterenol in comparable concentration is less effective in lowering the pressure, and *d*-epinephrine and adrenalone were practically ineffective. A particularly interesting observation has been that isoproterenol (Aleudrine, Isuprel) depresses the formation of aqueous humor and lowers the intraocular pressure to the same degree as does *l*-epinephrine, yet this drug lacks the vasoconstrictor and mydriatic properties of *l*-epinephrine. This contrast suggested that the manner in which both substances interfere with formation of aqueous humor is probably through some process other than through vasoconstriction and lessened blood supply, possibly through alteration of a metabolic process. This view should stimulate search for a hypothetical related substance having the postulated inhibitory effect on metabolism but devoid of vascular action. One chemically related substance, an oxidation product of adrenalin known as carbazochrome (Adrenosem), which was carefully examined, was unfortunately found to be devoid of influence on intraocular pressure and facility of outflow as well as on vessels.[53] On the other hand, naphazoline (Privine) has shown only slight pressure-lowering action, despite enthusiastic clinical claims for benefit in glaucoma, which scarcely seem warranted.[76] A related drug, tetrahydrazoline (Tyzine) has been described as a prolonged vasoconstrictor when applied to the eye, but no information on its effect on pressure has yet been provided.[51]

Sympatholytic drug action in lowering of intraocular pressure has, at least in the case of N,N-dibenzyl-β-chloroethylamine (Dibenamine), been established and now confirmed as an inhibitory influence on formation of aqueous humor.[44] The relation of its action to the inhibitory effect of a sympathomimetic drug such as *l*-epinephrine is not known. Although none of the sympatholytic drugs has come into widespread use in treatment of glaucoma, owing to various shortcomings, the possibility of discovering a clinically practicable sympatholytic agent has encouraged further search. In the case of one potential agent, N-phenoxyisopropyl-N-benzyl-β-chloroethylamine (Dibenzyline), unfortunately no appreciable reduction of intraocular pressure has been observed in normal eyes or in most glaucomatous eyes when moderately large doses are injected intravenously.[59] In the case of another sympatholytic agent, (6-acetoxythymyloxyethyl) dimethylamine hydrochloride, known as Opilon, a temporary decrease of pressure was induced in most cases of glaucoma following topical application, but the utility of the drug was limited by its irritative action on the conjunctiva.[81]

Certain substances which manifest complex pharmacologic properties and have conspicuous vasodilating effect when applied to the eye provoke a transient rise in intraocular pressure. Tolazoline (Priscoline) in human eyes and isoflurophate (D F P); Floropryl, and mechlorethamine (nitrogen mustard) in rabbit eyes have these properties.† Although the mechanism of their influence on the intraocular pressure is not known, such substances are of continuing interest and utility in studies of the regulation of intraocular pressure. Another substance of still more obscure function, calcium phosphorylcholine, has been described as raising the intraocular pressure following subconjunctival injection and to be useful in treatment of hypotony. This reported effect seems to merit more careful experimental investigation.[80]

Studies of the effect of succinylcholine on the intraocular pressure in cats and human patients have strongly supported the conclusion that it is the contraction of the extraocular muscles which causes the brief rise of intraocular pressure following intravenous administration of this remarkable substance.[67]

† References 96, 102, and 115.

Several drugs which have a relaxing or a sedative effect on the patient have been examined for influence on the intraocular pressure, but only slight effects have been found. Mephenesin (Myanesin, Tolserol) has been claimed to have a general relaxing effect on the patient, reducing the risk of vitreous loss during cataract extraction, but no paralyzing effect on the extraocular muscles and slight influence on intraocular pressure have been demonstrated.‡ Chlorpromazine (Megaphen, Largactil, Thorazine) similarly has been found to be a helpful adjunct to premedication for surgery and for relief of anxiety. Furthermore, when administered intravenously or intramuscularly in sufficient doses to cause a considerable fall of blood pressure, it has brought about miosis and convincing decreases of intraocular pressure, and advantage has been taken of this effect in treatment of acute glaucoma.§ Unfortunately, the effect on intraocular pressure is not maintained by repeated medication. Pentobarbital (Nembutal) and paraldehyde have each been found to cause decreases of intraocular pressure of approximately 3 mm. (mercury) in normal rabbits. The principal interest of this observation is that the decrease was found to be due exclusively to an increase in facility of aqueous outflow.[101] How this is accomplished remains a question.

In concluding this section on the influence of drugs on the intraocular pressure, attention is called to the publication during the past year of a review of the same subject covering fundamental aspects and not limited to any specific period.[34] This review is not likely to be of much interest or use to clinical ophthalmologists, but it may be useful to investigators contemplating research in this field. It provides a survey of anatomic, physiologic, pathologic, and methodologic details in relation to pharmacologic influences on intraocular pressure.

Steroid Hormones.—In the past year interest in the ophthalmic aspects of the steroid hormones seems to have subsided considerably, owing presumably to general satisfaction with the clinical and experimental evaluations already accomplished. Additional comparisons have been made of the relative efficiency of penetration of familiar steroids into the eye from surface application, and it appears agreed that cortisone penetrates into the anterior segment more effectively than hydrocortisone and that the free alcohols penetrate better than acetate esters which are commonly employed.‖ The influence of cortisone on wound healing has also received additional study, with the conclusion that it interferes with development of tensile strength in healing of corneal wounds in rabbits[80] but does not alter the healing process after fistulating operations for glaucoma or improve significantly the functional result.[43]

The advent of two new steroid hormones, prednisone (Meticorten, Deltasone) and prednisolone (Meticortelone, Delta-Cortef), is noteworthy because of certain advantages which they offer. These new hormones are derivatives of cortisone and hydrocortisone, respectively. They offer the advantages for systemic administration of causing less disturbance of sodium, potassium, and water metabolism than do the parent compounds. The effectiveness of the new compounds in controlling intraocular inflammatory conditions has been established in rabbits and patients, and it appears that effects similar to or superior to those of the older compounds may be obtained at lower dosage levels.¶

‡ References 6 and 105.
§ References 18, 33, and 60.
‖ References 42 and 66.
¶ References 54 and 79.

Antibiotics and Chemotherapeutics.—Several studies have been carried out comparing penetration of various antibiotics into the eye following topical or systemic administration.# Chlortetracycline (Aureomycin), oxyteracycline (Terramycin), and chloramphenicol (Chloromycetin) were found to reach effective concentrations in the cornea but not within the eye when applied topically. Tetracycline (Achromycin) penetrated poorly when applied locally and was irritating. Penetration into the eye following systemic administration appeared to be best for chloramphenicol but also good for tetracycline. In the case of erythromycin, bacteriostatic concentrations were achieved in the aqueous humor, but not in the vitreous, following oral administration of ordinary doses.[90]

Recommendations based on clinical rationale rather than systemic comparison have been made favoring N^1-dimethylacroylsulfanilamide (Sulfirgamide) and a mixture of polymyxin and bacitracin for superficial ocular infections.* The basis for the recommendation has been that these substances are, like many others, effective against pyogenic organisms, but they have an advantage of low allergenicity and they replace other antibiotics which may be reserved for more serious conditions. For preparation of self-sterilizing collyria the incorporation of one of these antibiotics, polymyxin B sulfate, has been demonstrated in careful experimental work to provide more rapid and reliable results, particularly in eliminating Pseudomonas aeruginosa, than do the usual additions of benzalkonium or chlorobutanol.[93]

Isoniazid, a chemotherapeutic agent which has proved valuable in treatment of pulmonary tuberculosis, has been evaluated for use in ophthalmic therapy. In rabbits this drug has been found to have low toxicity and to penetrate readily into the anterior segment from the conjunctival sac and into the posterior segment from the circulation. It is therapeutically effective against tubercle bacilli introduced into the eyes of nonimmune nonallergic rabbits but not against other bacteria. It is more rapidly effective than either streptomycin or aminosalicylate.[59] Evaluation of the therapeutic effect of isoniazid in the eyes of patients is much more difficult. Identification in patients of just which ophthalmic diseases are tuberculous is highly uncertain, and some of the processes which might be termed tuberculous may show spontaneous improvement. Despite these difficulties, clinical evaluations have been carried out, and it has been observed that half or more of the patients having choroiditis, periphlebitis, and anterior scleritis with uveitis improved while under treatment with isoniazid.† On the other hand, in a portion of the cases of periphlebitis bleeding became worse.[111] Some indication of a toxic effect on vision has been observed in patients who developed optic neuritis and optic atrophy following intraspinal injections of large amounts of isoniazid in treatment of tuberculous meningitis, but this complication has rarely occurred when the drug has been given orally.‡

Local Anesthetics.—No notable new developments have been reported, but various comparisons have been made of efficiencies and deficiencies of the numerous local anesthetic agents now available. In general the differences have been slight, but several substances having essentially the same anesthetic efficiency as tetracaine (Pontocaine) have been found to be appreciably less irritant or discomforting to the patients; examples are ambutoxate hydrochloride (Sympocaine),

References 1, 12, and 41.
* References 3 and 107.
† References 59 and 111.
‡ References 13 and 103.

2-diethylaminoethyl-3-amino-4-propoxybenzoate hydrochloride (Ophthaine) and Dorsacaine (benoxinate).§ These drugs all have close chemical similarities.

An ingenious method for evaluating the irritancy of local anesthetics, as well as of other drugs, has been devised, taking advantage of the vulnerability of the endothelium of the cornea and the conspicuous indications given by the rest of the cornea when the endothelium is injured.[99] The method consists of injecting the solution to be tested into the anterior chamber of rabbit eyes and observing the degree of corneal clouding resulting within 24 hours. The test is said to be more sensitive and to parallel clinical estimates of irritancy better than other animal tests.

Miscellaneous.—Selenium sulfide (Selsun) ointment for treatment of marginal blepharitis was found to have no superiority over old-fashioned ammoniated mercury ointment and to have the possible disadvantage of causing occasional transient keratitis and blepharitis.[114]

A possible basis for employing testosterone injections in treatment of keratitis sicca was advanced by experiments in which this medication was shown to cause an increase in weight of the lacrimal glands in rabbits.[91] However, an increase in tear production was not demonstrated.

In an especially sensitive method for assaying ganglion blocking activity, advantage has been taken of the protrusion of the eyeball of the rat which follows stimulation of the cervical sympathetic in order to obtain a measure of transmission through the superior cervical ganglion and of the influence of minute amounts of drugs thereon.[52]

For testing for myasthenia gravis in patients with malfunctioning extraocular muscles, results are claimed to be more reliable from injection of edrophonium (Tensilon) than by use of the standard agent, neostigmine.[14]

Treatment of various ocular conditions by intramuscular injection of the enzyme trypsin has been much publicized in lay literature, but in the ophthalmic literature insufficient evidence has been reported to permit adequate evaluation. The only ophthalmologic reports have come from one group of investigators, and their observations are presented without adequate control.[48] The conditions in which benefit is claimed, such as in black eyes, hyphema, uveitis, and vitreous hemorrhage, are conditions in which spontaneous improvement may be expected. Additional evidence presumably will soon be forthcoming.

Reviews.—A comprehensive survey and review of general principles of ophthalmic pharmacology, including a summary of current information on drug actions, has recently been published. This should be useful particularly to those in postgraduate ophthalmic training.[65] A review limited to physiology and pharmacology of intraocular pressure[34] has been described at the end of the section concerning drugs which influence the intraocular pressure.

Ophthalmic Toxicology: Anterior Segment

In this review, ophthalmic toxicology will be subdivided into toxicology of the anterior segment and toxicology of the posterior segment. The subject has been thus subdivided for convenience in presentation because injuries of the anterior segment are usually induced in a different manner from those of the posterior segment, the one by direct contact and the other through systemic intoxication.

§ References 23 and 69.

Acid and Alkali Injuries.—The intact corneal epithelium withstands a rather wide range of pH without injury, but above pH 10 and below pH 4 an increase of permeability becomes detectable.[72] More extreme conditions of pH of course cause destruction of the epithelium. When rabbit eyes are exposed briefly to a low pH (one minute to 1 N hydrochloric acid), the ascorbic acid content has been found to drop immediately but to return to normal in about five days.[39] Although the basis for this change or its significance has not been established, it appears to be a result of loss of ascorbic acid from the cornea. Since normally the epithelium contains most of the ascorbic acid in the cornea, it would be desirable to ascertain whether the changes observed are correlated with injury and subsequent regeneration of these particular cells. Experimental therapeutic administration of ascorbic acid by drop and subconjunctival injection following alkali burning of the cornea has not been found to be helpful.[113]

Injury of the corneal stroma by alkalies has been demonstrated to be governed by the pH of the alkali, regardless in most instances of the nature of the cation. As part of the reaction at high pH, the cornea takes up and binds cations, apparently in association with the collagen, and dissociates or releases some of its acid mucopolysaccharide.[35] In the case of lime burn of the cornea, it had previously been thought that the mucopolysaccharide was precipitated in the cornea, but this is found not to be so; following exposure to lime the mucopolysaccharide is rendered more readily extractible than normal.[35]

In treatment of alkali burns, prolonged washing with water is required to regain neutrality because the binding of the cations to the cornea is only slowly reversible and there is attendant regeneration of hydroxyl ions. Attempting to accelerate the process by irrigation with dilute hydrochloric acid (pH 1 and 2) was found to make the injury worse. Irrigation with a neutral solution of edathamil sodium (sodium ethylenediamine-tetraacetate) was found to speed removal of calcium from lime-burned rabbit corneas, but it did not appreciably modify the associated corneal opacity. These lime burns in rabbits were comparable to injuries of the deep stroma in human eyes and not to superficial lime burns with opacification limited to the region of Bowman's membrane, such as in human eyes are readily eliminated by edathamil sodium solution.[35]

In experimental treatment of acid and alkali burns in the eyes of rats, application of calsulfhydryl (Hydrosulphosol) was found to be of no help. In fact in some cases this treatment led to slower healing and greater corneal opacification than using no treatment at all.[7]

Detergent Injury.—An interesting instance of corneal injury by an anionic detergent present in a commerical skin cleansing preparation, pHisoHex, was investigated by testing in rabbit eyes. Severe corneal edema was induced, and recovery took several weeks. The hexachlorophene in the mixture was shown to be relatively innocuous, and responsibility for the injurious action was put upon the detergent, a substance having the commercial names Entsufon and Triton, chemically an alky-aryl polyether sulfonate.[16] Unfortunately, the report of these findings was marred by a mistake to which I wish to call attention. The name of the detergent given by the authors was accidently changed in publication to that of a quite different substance. Repeatedly in the paper appears the name trinitrotoluene, which actually is the name of the high-explosive familiarly known as T.N.T., an entirely different substance chemically and toxicologically from the detergent which was identified as the cause of the corneal damage. It is to be hoped that this error will not be perpetuated in the literature.

Miscellaneous Injuries.—An interesting sort of corneal epithelial erosion has been caused by an ophthalmic ointment containing 2% of certain polyethyleneglycolethers.§ Repeated application of the ointment to the eyes of patients and rabbits led to hypesthesia, keratitis epithelialis, and finally almost complete loss of epithelium. Most eyes recovered without scarring when use of the ointment was discontinued. The responsibility of the polyethylenglycolethers for the injurious action was adequately established by testing on rabbits, but, unfortunately, little information was given regarding the molecular weight or chain length of the compounds involved. However, it does appear pertinent that they were added to the ointment because of a known local anesthetic action on the cornea. It is highly probable that these compounds were nonionic surface-active agents.

An unusual sort of keratitis epithelialis characterized by the presence of vacuoles in the epithelium, reminiscent of those induced by butanol, has been observed to result from oral administration of a new antibiotic drug in treatment of tuberculosis.[87] Fourteen patients receiving pyridin-3-aldehyde thiosemicarbazone for 7 to 11 weeks in combination with isoniazid developed this ocular complication. Fortunately, the symptoms associated were mild, and the epithelium returned to normal in two to four weeks after discontinuation of the medication. Presumably the isoniazid was not responsible, since it has been so widely employed without other known corneal disturbance.

Clinical reports of corneal and conjunctival injuries other than those already discussed have not recently brought forth any particularly noteworthy observations. An additional 12 cases of severe corneal damage from tear gas have been described,|| and additional observations have been made on the keratoconjunctivitis which is induced when emetine hydrochloride is splashed into the eye.[29] An uncommonly severe instance of keratitis going on to corneal ulceration following prolonged industrial exposure to the manufacture of hydroquinone has been reported,[58] and unusual instances of severe corneal damage have been ascribed to contact with a sulfocarbolic-zinc solution [110] and with a spice related to ginger, Rhizoma galange.[46]

Experimentally, the toxicity of various substances to the endothelial side of the cornea has been examined by injection into the anterior chamber. Induction of corneal edema has been the criterion for injury. In a preceding section of this review concerned with the pharmacology of local anesthetics the use of this procedure was described for the practical testing of the irritancy of drugs. The mechanism of injurious action has also been examined experimentally, although in a rather narrow sense. Test substances were injected into the anterior chamber of enucleated rabbit and cat eyes, and after incubation at 31 C for 16 to 20 hours in a moist chamber the water content of the corneas was determined by excising and weighing them. Comparison was made with control eyes injected with salt solution which presumably was nearly isotonic with the test solutions. A wide variety of substances was tested in this manner, and an attempt was made to relate abnormal hydration to inhibitory influences on glycolytic activity, cholinesterase activity, and metabolism of adenosine triphosphate (ATP) in the cornea. Some apparent correlations were observed, but the significance of the work seems to have been unnecessarily limited by the preoccupation of the investigator with an assumed metabolic process for movement of water from cornea to aqueous

§ References 85 and 86.

|| References 45 and 116.

humor. Unfortunately, other pertinent factors such as the physical integrity of the endothelium and its semipermeability were not mentioned, nor was attention given to the potential influence of the various test solutions on the turgescibility of the stroma of the cornea, in the event that they gained access to it by injuring the endothelium.[83]

Much testing of the irritancy or danger of chemicals to the eye is regularly carried out to safeguard against hazardous handling of these substances. Unfortunately only a small fraction of the results of such tests ever become published. Among those substances reported on in the past year, particularly severe effects on the cornea have been ascribed to gaseous chlorine trifluoride,[49] to liquid trimethyltrithiophosphites and triethyltrithiophosphites,[95] and to a variety of organic isocyanates.[97] Chlorine trifluoride was found to be extremely corrosive and irritating, causing severe corneal ulcers in experimentally exposed dogs.[49] The alkytrithiophosphites were so toxic that 0.1 ml. in the conjunctival sac of rabbits caused death in most animals and in the survivors induced corneal opacification which cleared in about a month.[95] Various isocyanates, particularly toluene diisocyanate, was found to be very irritating to the eyes and respiratory tract during industrial and experimental exposures to low concentration of the vapor.[97]

Smog Irritation.—The stinging and burning sensation of the eyes which is associated with the smog of some large cities (particularly Los Angeles) has occasioned little comment in ophthalmic journals, probably because no serious consequences have been observed. However, because of the public nuisance aspect, the cause of the discomfort has been under investigation by industrial and public health agencies. As yet the substances responsible for the eye irritation have not been identified. Current opinion is that either hydrocarbon (petroleum) compounds in a highly reactive free radical condition, or ozone, which in Los Angeles smog is found in exceptionally high concentration, may be responsible.[22] The smog atmosphere contains a complex reaction mixture in which sunlight provides energy for photochemical reaction of oxides of nitrogen with hydrocarbons to produce ozone. Precise identification of the irritating substance or substances is difficult because of the small quantities, high reactivities, and probable short lives involved.

Induction of Iris Cysts by Miotics.—Confirmatory observations have been made on the induction of pigmented cysts at the pupillary margin by chronic local administration of isoflurophate[70] and development of similar cysts in patients under treatment with pilocarpine, diethyl *p*-nitrophenyl phosphate (Mintacol), physostigmine (eserine), and prostigmin reestablish that this is a general effect of miotics and is not peculiar to isoflurophate.¶

Inductions of Cataracts by Chemicals.—Although opacities of the lens are most often induced by systemically administered poisons, occasionally chemicals applied locally are responsible, but usually in association with severe damage of the cornea and conjunctiva. It is somewhat surprising to learn of the occurrence of anterior subepithelial lens opacities following therapeutic cauterization of the cornea with 20% zinc sulfate in three instances; these opacities appeared at the earliest 12 days after treatment.[84]

In the case of cataracts induced experimentally by systemic poisoning, two new causes have been discovered, and further observations have been made on

¶ References 20 and 28.

the well-known cataractogenesis by alloxan.# Iodoacetic acid administered to rabbits was known to cause severe damage to the retina, but now it has also been shown to cause atrophy and fibrosis of the iris, ciliary body, and choroid, as well as posterior cortical cataracts resembling radiation cataracts.[19] Another instance of radiomimetic cataractogenesis has been observed in rats given busulfan (Myleran). Injury of the lens occurred at considerably higher dosage of this drug than is employed clinically in treatment of myeloid leukemia. These new observations on iodoacetic acid and busulfan suggest that close attention might well be given to the possible ocular effects of the many other cytotoxic agents currently being tested to combat malignancy.

Ophthalmic Toxicology: Posterior Segment

Retinal Effects of Excessive Oxygen.—Since earlier dramatic demonstrations that abnormal concentrations of oxygen have a vital role in the development of retrolental fibroplasia, the literature offers a review[4] and an extensive symposium on the subject[104] but not a great deal of new information. It has been determined that the abnormalities induced by exposure to excessive oxygen occur predominantly in the ocular tissues which are undergoing the greatest development at the time of exposure.[40] The vaso-obliterative effects of oxygen on immature retinal vessels is not influenced by the sympathetic innervation of the eye,[21] but experimental detachment of the retina does interfere with this effect.[5]

Clinically, the opinion has been expressed that appearance of retinal edema is the earliest sign of threatened retinopathy and that this is reversible.[71] Evidence has accumulated that for best results withdrawal of premature infants with retrolental fibroplasia from high oxygen atmosphere should be gradual rather than sudden.[11] Attempts to influence the disease by means of chlorpromazine have given no definite results.[73]

Most of the attention concerning retinal disturbances from oxygen has been directed to the developmental abnormalities induced in the very young, but significant toxic effects are known to occur also in adults. Functional disturbance of vision in human beings has previously been reported to follow chronic breathing of high concentrations of oxygen, and it has been shown that exposure of adult albino rabbits to pure oxygen for 40 hours causes extensive degeneration of the rods and induces edema of the ciliary body and iris.[75] Possibly this is related to the disturbance of vision previously known to occur in human beings as the result of prolonged breathing of high concentrations of oxygen, but the disturbance in human eyes has been reported to be reversible.

Toxic Amblyopias and Blindness in Patients.—Additional observations have been reported on disturbances from sulfonamides,[106] quinine,* hexamethonium,[17] and organic arsenicals.[78] Few instances of toxic amblyopia from sulfonamides have been reported in the literature, and in the course of 10 years only four cases have been observed at the Mayo Clinic. In these cases optic neuritis has been associated with use of small doses of various sulfonamides, and there has been good recovery in all cases.[106] A dramatic instance of sudden bilateral loss of vision and subsequent optic atrophy in a hypertensive patient following intravenous injection of hexamethonium chloride has been described, the second case of this sort reported.[17]

References 15, 74, and 77.

* References 30 and 68.

Experimental Methyl Alcohol Poisoning.—One of the problems in attempting to establish how methyl alcohol causes blindness and how best to treat this poisoning has been the fact that in human beings the effect is different in several respects from that in most experimental animals. However, it has recently been shown that in monkeys the action more closely resembles that in human beings. It is not certain that the results are identical. In monkeys it appears that severe disturbances of retinal function and damage of the central nervous system may be induced even though acidosis is prevented by administration of sodium bicarbonate.[88] Clinical experience, on the other hand, has led to widespread acceptance of the belief that the severity of ocular and systemic intoxication by methyl alcohol is greatly alleviated by correcting the acidosis. Experimentally, evidence tending to incriminate formaldehyde as the toxic intermediate in methyl alcohol poisoning has come from electroretinographic studies on monkeys, but even by prolonged intravenous administration of formaldehyde the effects of methyl alcohol on the central nervous system have not been reproduced.[88]

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News and Comment

ANNOUNCEMENTS

Fellowships in Ophthalmology.—Twelve ophthalmologists throughout the nation will serve on committees to select recipients for the Residency Fellowships in Ophthalmology recently established by the Guild of Prescription Opticians, it has been announced by Galen B. Kilburn, of Atlanta, President of the Guild.

They are Alson E. Braley, M.D., Iowa City; F. Phinizy Calhoun Jr., M.D., Atlanta; David G. Cogan, M.D., Boston; Alfred J. Elliot, M.D., Toronto, Canada; R. M. Fasanella, M.D., New Haven, Conn.; R. E. Hannon, M.D., Cleveland; Michael J. Hogan, M.D., San Francisco; Frank W. Newell, M.D., Chicago; Shaler Richardson, M.D., Jacksonville, Fla.; Benjamin M. Rones, M.D., Washington, D.C.; Theodore E. Sanders, M.D., St. Louis; Harold Scheie, M.D., Philadelphia.

The Guild offers six new Fellowships every year, one in each of six areas, with an $1800 stipend for the three-year residency.

Sixth Argentine Congress of Ophthalmology.—The Executive Council of the Sixth Argentine Congress of Ophthalmology, constituted by Dr. Carlos S. Damel, President; Prof. Paulina Satanovsky and Dr. Nicholás Gonzalez Llanos, Vice-Presidents; Drs. Jorge Balza and Héctor R. Pícoli, Prof. Juan M. Vila Ortiz, and Dr. Edgardo Manzitti, Secretaries, and Dr. Moisés Brodsky, Treasurer, with the honorary presidency of Dr. Esteban Adrogué and Professors Raúl Argañaráz, Diego M. Argüello, Jorge L. Malbran, and Alberto Urretz Zavalía, have announced that the Congress will be held in the city of Mar del Plata, Argentine Republic, April 9-14, 1957.

The official themes, Cornea (Acquisitions after 1935) and Vertical Strabismus, have been discussed in the following papers:

Dr. A. Ferrer Arata: Morphology of the Cornea: Anatomy and histology
Dr. Julio Arouh: Semiology of the Cornea
Dr. Dante Dolzani: Physiopathology of the Cornea
Dr. Carlos Laje Weskamps: Pathologic Anatomy of the Cornea
Dr. Virgilio Victoria: Pathology of the Cornea
Dr. Alejandro Salleras: Clinical Treatment of the Corneal Diseases
Dr. Pedro F. García Nocito: Surgical Treatment of the Cornea
Dr. Alberto C. Cremona: Hereditary Diseases of the Cornea
Dr. Jorge C. Zambrano: Legal and Social Medicine in Corneal Affections
Dr. Francisco Bellouard Ezcurra: Etiology, Pathogenesis, and Diagnosis of Vertical Strabismus
Dr. Alberto Urretz Xavalía: Treatment of Vertical Strabismus.

All correspondence should be sent to Dr. Jorge Balza, Secretary of the Sixth Argentine Congress of Ophthalmology, Post Office No. 2699, Buenos Aires, Argentina.

Pan-Pacific Surgical Association Congress.—The Seventh Congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii, Nov. 14-22, 1957. All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

An outstanding scientific program by leading surgeons with sessions in all divisions of surgery and related fields promises to be of interest to all physicians.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Room 230, Young Building, Honolulu, Hawaii.

Books

Acta XVII concilium ophthalmologicum, 1954, Canada, United States of America. Price, 20.00. Three volumes, cxxxix, 2090 pages. Toronto, University of Toronto Press, 1955.

It is something of an adventure to read the transactions of all the International Congresses of Ophthalmology, for the path of this organization has not been easy and each meeting has been plagued with unique problems. At times it seemed that the very life of the organization was threatened, that it would never again function. Fires, wars, revolutions, diplomatic red tape, narrow-minded nationalism, and, strangely enough, from time to time even out-and-out apathy have been the problems the organizations committees of the past have had to face. Yet these committees have planned and brought into being 17 meetings, and they have in spite of all obstacles, new and old, made each meeting more interesting, more popular, and wider in scope than the preceeding meeting. No mean feat, indeed.

No less important and difficult have been the tasks of the editorial committees, who have been charged with the responsibility of providing for the public an accurate record of the congressional proceedings. In preparing the Acta of the XVII Congress the editorial committee has lived up to the standards set by its predecessors, and in some respects has done a superior job.

For the sake of continuity it was decided to use a format similar to that used for the Acta of the London Congress of 1950. The result is three handsome volumes bound in dark green cloth with gold stamped lettering. The paging is continuous for the three volumes, and each volume has its own table of contents. The illustrations on the whole are excellent, a good quality of paper having been used. One omission is a subject index; only an index of the contributors is provided. It is inevitable that a few errors should have slipped by the proof reader (metabolic appears as hetabolic), but these are so few as to be conspicuous by their presence. It is amazing that such a fine job of editing and publishing should have been done when one learns of the many obstacles which faced the editorial committee.

Volume I of the Acta opens with a section that contains the statutes, minutes of the meetings, and lists of the officers of the International Council of Ophthalmology and the associated societies. This is followed by the names of the committee members of the XVII Congress, a resumé of the opening ceremonies in Montreal and New York, a description of the scientific exhibits, the motion picture program, a description of the new instruments that were presented, the social program, the closing ceremony, and the roster of the official delegates, full members, and associate members of the Congress.

The remainder of Volume I and all of Volumes II and III are devoted to scientific papers. More than 200 papers appear. About a fourth of them are in languages other than English. Excellent summaries in three languages, Spanish, French, and English, are given for the majority of the papers. This means that those readers whose native language is English and who are not masters of a second language have in the three volumes of the Acta an unparalled opportunity to meet the minds and thoughts of ophthalmologists from all over the world. This complete absence of barriers is the great product of the International Congresses and their printed proceedings.

The XVII Congress had two official subjects: "The Etiology of Uveitis" and "Primary Glaucoma." The papers on the second subject are supplemented by a symposium on "Tonography and Aqueous Humor Dynamics." A second symposium, "The Transparent Media of the Eye," was divided into two parts: "The Cornea" and "The Lens and Vitreous." There was one panel discussion on "Virus Diseases of the Eye" and another on "The Prevention and Management of Retrolental Fibroplasia." This second panel discussion gave investigators from several countries a long-awaited opportunity to correlate their findings and perhaps to write an end to a tragic chapter of present-day medicine.

At the end of Volume III appear those papers that were read before the International Organization Against Trachoma and the International Association for the Prevention of Blindness. These two groups held their meetings at the same time as the Ophthalmic Congress.

All the papers described above account for less than one-third of the total papers presented. It is impossible in a short review to list the titles or even the subject matter of the remaining papers, for the three volumes with their 2090 pages constitute what might be termed an encyclopedia of ophthalmology. Select almost any subject and at least one paper will be found.

It is true that a certain unevenness in the quality of the material exists, but this is always true of a composite work. It is true that certain subjects have received more attention than perhaps they deserve, but this, too, is not unexpected. When one reads or consults the Acta of the XVII International Congress of Ophthalmology one or two thoughts should be kept in mind: Two hundred voices are speaking on the one broad subject of ophthalmology. The small amount of dissonance that is heard is not important. What is important is the speaking itself and that a permanent record of an unusual occurrence has been provided.

A limited number of the sets (three volumes) are available from the office of W. L. Benedict, M.D., 100 First Avenue Building, Rochester, Minn. Price, $20.00 postpaid. The publisher's price is $30.00.

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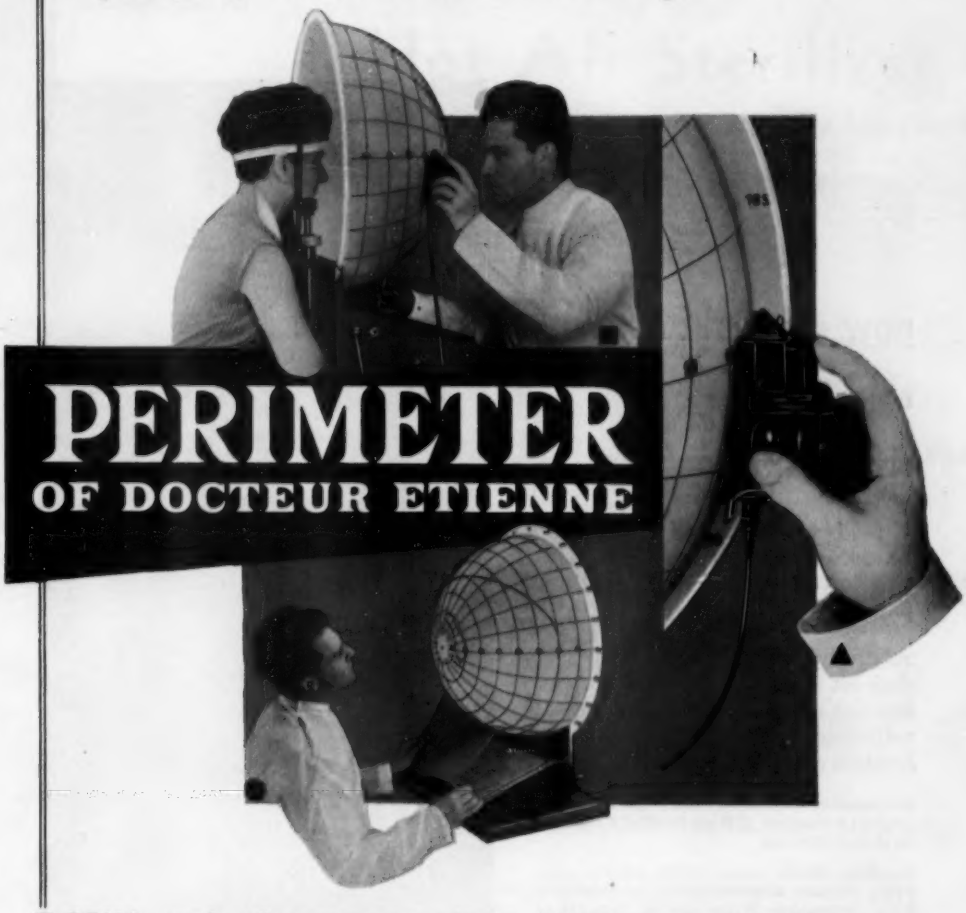

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*Schimpf, H. E., Jr., and Swan, K. C.: A. M. A. Arch. Ophth. *51*:663 (May) 1954.

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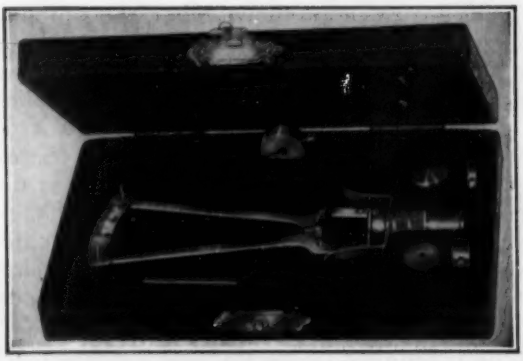

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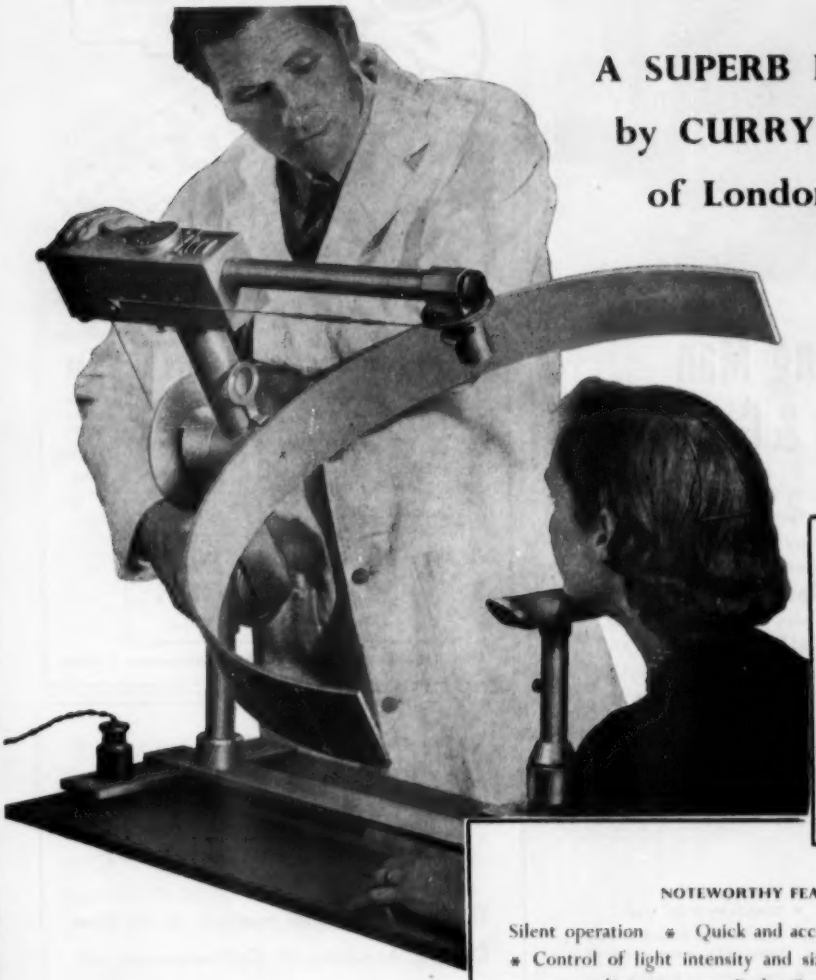

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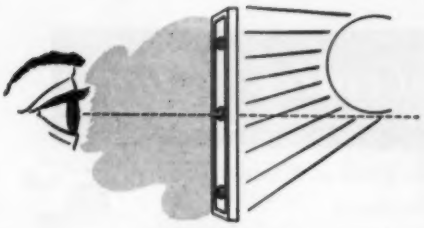

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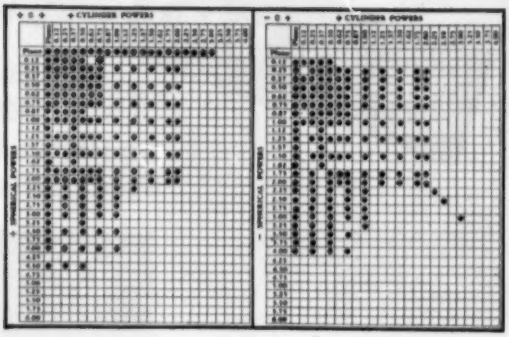

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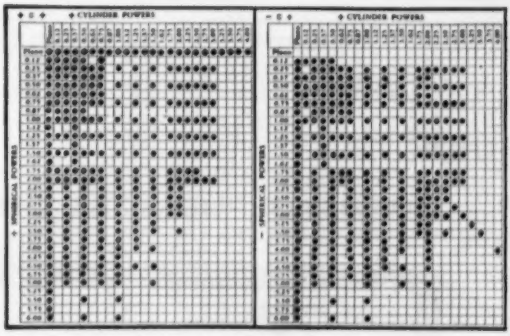

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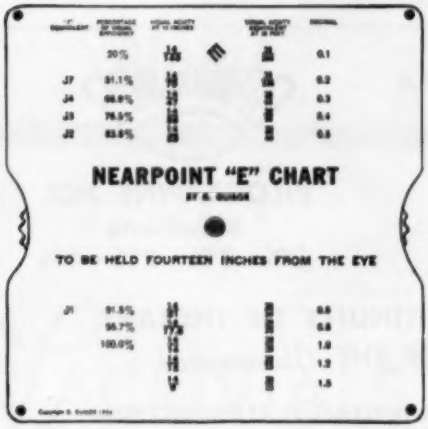

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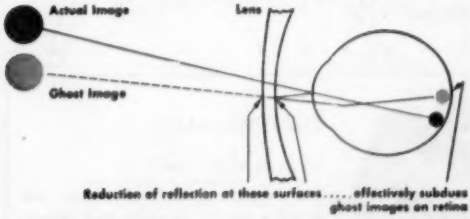

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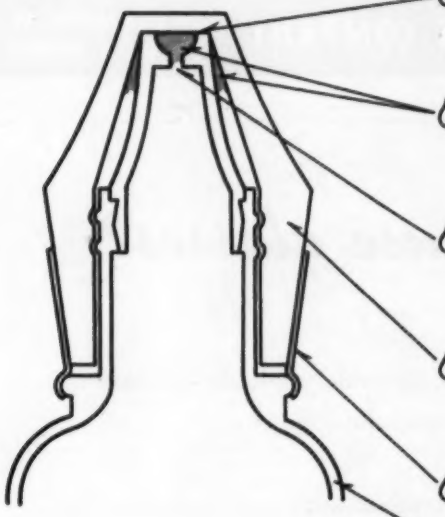

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5-5-55: Right vision with 4-12-55 Rx = 20/20. Manifest O.D. +10.00Dsph. ○ +1.50Dcyl. ax 105 = 20/15+. Again, patient was allowed to retain former lens until the new Rx in CATAREX T was ready.

5-31-55: Right vision with 5-5-55 Rx = 20/50. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 60 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

7-6-55: Right vision with 5-31-55 Rx = 20/20+. Manifest O.D. +10.00Dsph. ○ +1.00Dcyl. ax 75 = 20/15+. Rx Right: Manifest findings in CATAREX T. Left: lens to balance.

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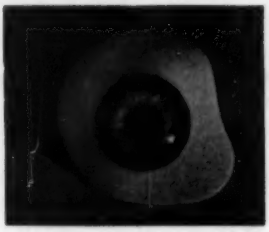

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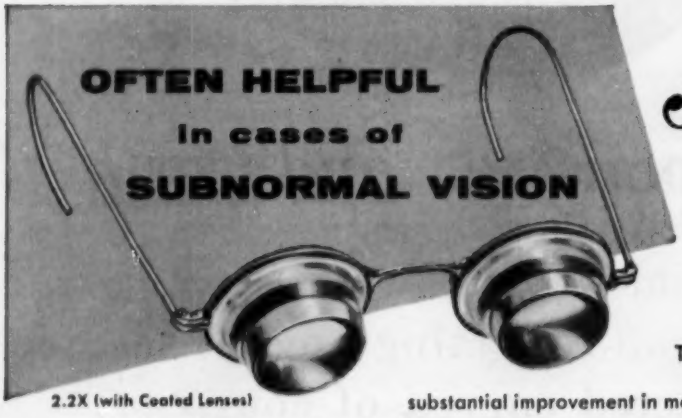

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References: Hogan, M. J., Thygeson, P. and Kimura, J., Arch. Ophth. 53:165, (Feb.) 1955.

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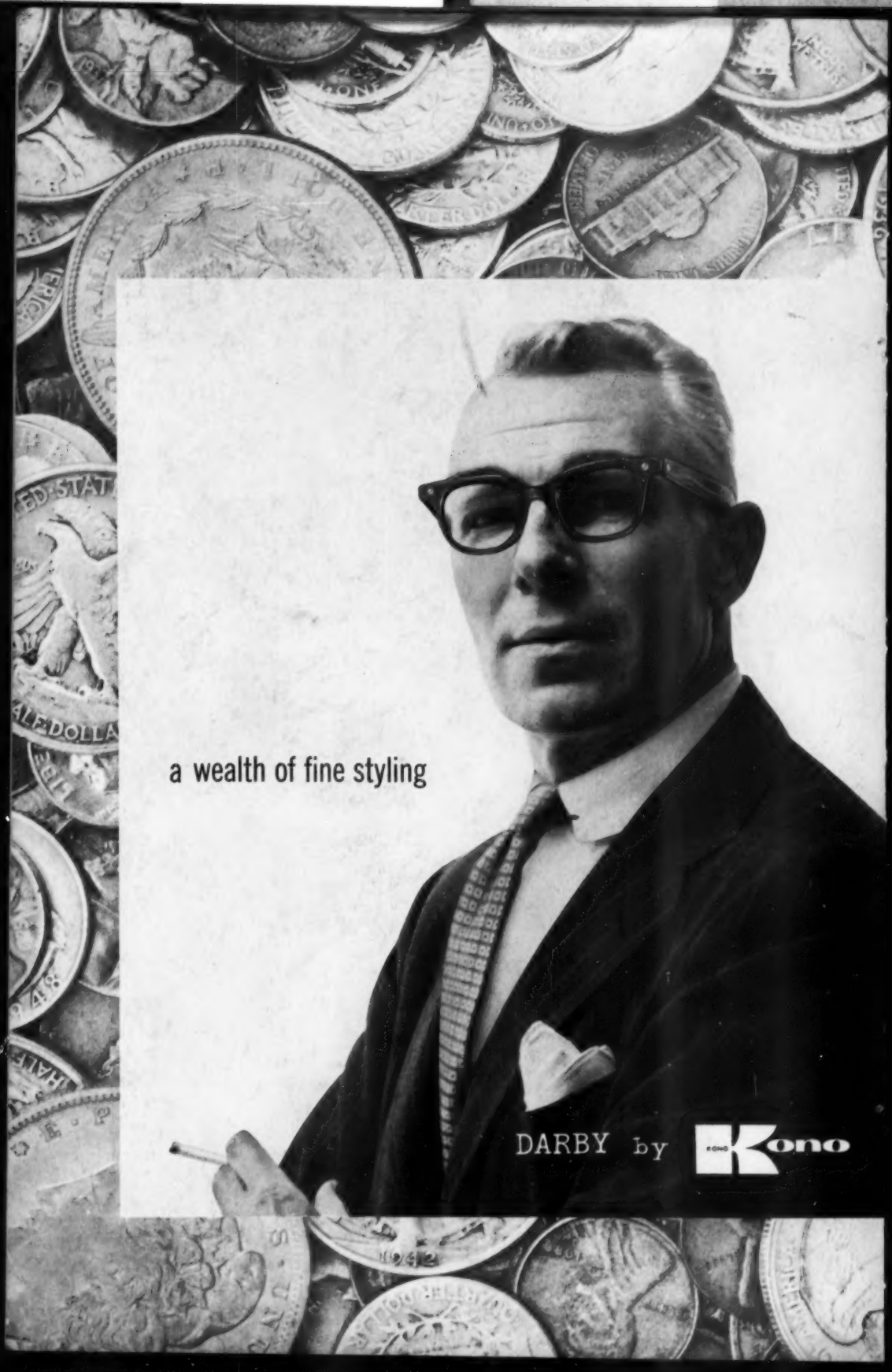
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